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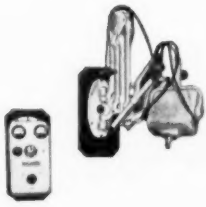

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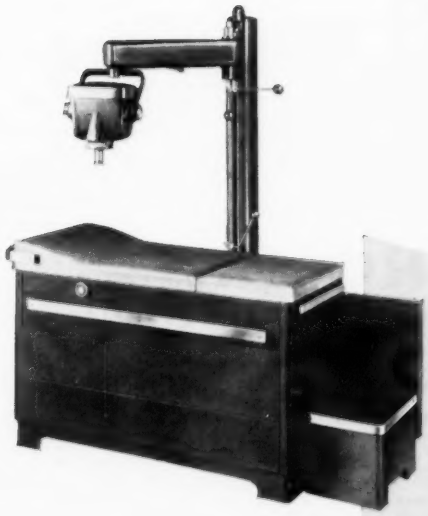

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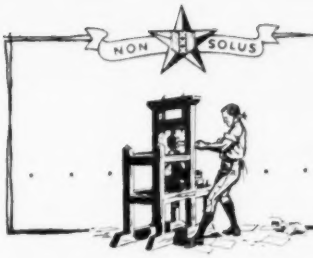

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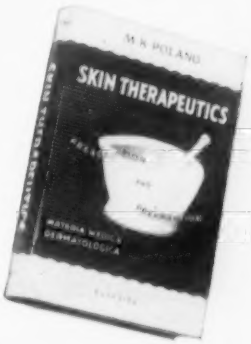

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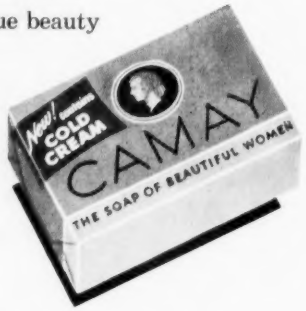

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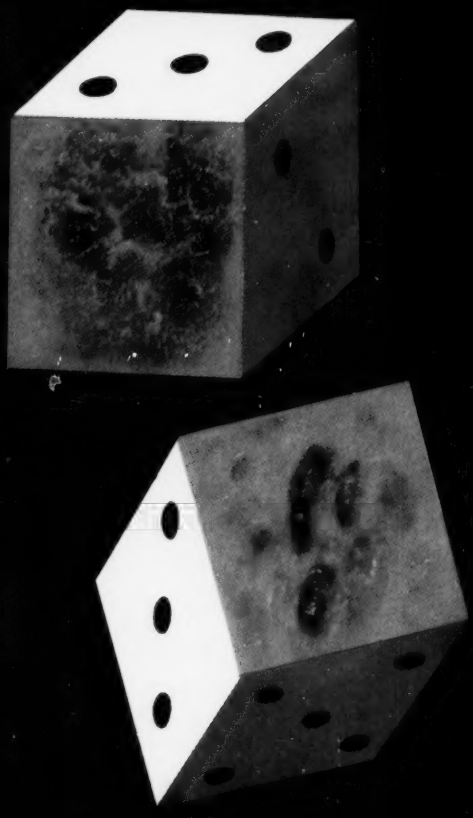

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2. Perrin, S. R.: Clinical Safety of Polysorb. Postgrad. Med. 8:485, 1950.

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Archives of Dermatology and Syphilology

VOLUME 69 JUNE 1954 NUMBER 6

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DERMATITIS OF THE FEET DUE TO SHOES

HARRY SHATIN, M.D.
AND
MILTON REISCH, M.D.
BRONX, N. Y.

INTRODUCTION

A RECENT article by Kierland[1] on the subject of military dermatology emphasizes the importance of dermatitis of the feet, with the many disabling weeks of illness that can ensue. He underlines how very little effective research in the prevention and cure of these dermatoses has been undertaken to date. We, in dealing with a civilian population, have also been struck by the large number of patients seen with disabling dermatosis of the feet, disabling enough to warrant hospitalization. We have seen patients who have suffered recurrent attacks of dermatitis of the feet for years. To appreciate the real problem not only must one see the patient who cannot walk because of localized, oozing, painful lesions of the feet, but one must also see the patient who has developed a secondary generalized dermatitis. One must also see such patients with the cellulitis, lymphangitis and lymphadenitis, thrombophlebitis, and even nephritis due to secondary infection of the local dermatitis of the feet and also the chronic lymphedemas of the legs due to recurrent lymphangitis and lymphadenitis.

Incidence.—In reviewing the admissions to the Dermatology Section of the Veterans Administration Hospital (Bronx, N. Y.) for the five-year period 1947-1951, we found that of a total of 2,243 admissions approximately 20% were due primarily to conditions of the feet variously diagnosed as dermatophytosis (13%), dermatitis venenata due to shoes (1.9%), eczema (1.5%) and many miscellaneous pedal conditions. It is understood that in the V. A. Hospital we are dealing essentially with an adult male population and our findings have no general statistical value, since we cannot allow for variations in women and children. Moreover it is important to note that in this paper we are discussing only hospitalized cases. The 1.9% represents 42 admissions to the hospital because of a dermatitis of the feet so disabling as to completely incapacitate the patient and render him bedridden. When we realized that 1 out of every 10 cases hospitalized because of a dermatologic condition of the feet was diagnosed as contact dermatitis due to shoes, we reviewed the charts of the latter cases in more detail.

Irregular Patch Test Reactions.—We found it difficult to establish a definite pattern of sensitivity in studying the charts. There were positive reactions to patch tests performed with various parts of the patients' shoes. Shoe lining, leather, inner sole, heel pad, and other parts of the shoe were capable of provoking positive skin

From the Dermatology and Syphilology Section, Medical Service, Veterans Administration Hospital.

reactions on patch testing. In any one patient there were noted positive reactions to a single substance or a group of substances. The individual patients appeared to react to different individual substances or groups of substances. There appeared to be no common antigenic agent among the various substances producing positive patch test reactions in any one individual. It was also noted that some patients did not have constant reactions but would have both positive and negative reactions in a variable fashion when tested with what was considered to be the identical part of

Fig. 1.—*A*, early contact dermatitis involving the dorsal surface of the big toe with beginning spread to the adjoining toes. *B*, more extensive contact dermatitis showing involvement of dorsal surface of foot and interdigital webs. Note excoriations on left foot indicative of the severe pruritus frequently encountered.

the same shoe. Attempts at explanation of these variable results were found in the charts. The positive reactions to several substances in one individual were glibly explained by multiple sensitivities. The variable responses to the same substance in one individual were explained by poor testing technique, or by localized skin sensitivity with resultant negative patch test reactions at a distance from the foot but positive reactions when the patch tests were performed close to the affected area of skin.

It was also noted in reviewing the charts that a certain number of patients had negative reactions to patch tests in a consistent fashion even though there was no clinical doubt that the patient had a dermatitis due to sensitivity to materials present in the shoes. In favor of the clinical diagnosis were both the appearance of the dermatitis, exacerbations coinciding with the wearing of shoes, and remissions apparently induced merely by removing the shoes.

Clinical Pattern.—In contrast to the irregular pattern of sensitivity based upon patch test reactions there appeared to be a fairly characteristic clinical picture in the majority of cases of shoe dermatitis both as to the site of the onset of the dermatitis and its evolution.

Most patients had a dermatitis of the anterodorsal portion of the foot. The dermatitis usually started on the dorsal surface of the big toe as a mild erythema with scaling (Fig. 1*A*), gradually became vesiculated, and at the same time showed a tendency to involve the backs of the adjoining toes. In some cases the dermatitis remained localized to these areas; in others there was gradual involvement of the distal half of the dorsum of the foot (Fig. 1*B*); in still other cases the interdigital webs were involved also, with spread in a few cases to the plantar surface. The dermatitis either remained unilateral or involved the dorsal surface of the other foot in a similar fashion. The involvement of the second foot was almost simultaneous in some cases or occurred after weeks and even months in others. When the involvement became extensive, the clinical picture was that of an intensely erythematous, exudative process covering the entire anterior half of one or both feet, usually only the dorsal surfaces but sometimes extending to the soles, (Fig. 2*A*). The involved areas were macerated, denuded, edematous, and secondarily infected.

One patient had involvement of the sole, featured by erythema, vesiculation, denudation, and weeping as the only manifestation of the dermatitis (Case 42).

A third form of dermatitis in our series was the type with vesicular, erythematous, pruritic lesions localized to the heel (heel pad type). We had three examples of this type (Cases 8, 9, 17).

The dermatitis was usually associated with severe pruritus. Several patients were hospitalized with only a mild dermatitis on the foot but with a severe cellulitis and lymphadenitis due to secondary infection precipitated by scratching.

In addition to the dermatitis of the feet some patients developed an "id"-like reaction of the hands and forearms. This was usually in the nature of a pruritic, vesicular eruption of the palms and sides of the fingers (Fig. 2*B*), sometimes in the form of erythema and scaling which spread to involve the forearms. These "ids" would appear simultaneously with the pedal dermatitis or develop later in the course of an exacerbation.

A certain number of cases led to confusion in diagnosis by presenting a typical picture of dermatophytosis of the soles and interdigital webs with extension onto the dorsum of the feet. Fungus mycelia were demonstrated or the dermatophyte was cultured from skin scrapings in some of these cases. These would ordinarily have been classified as dermatophytosis and treated as such. After we had become aware of the predilection of contact dermatitis due to shoes to involve the dorsum of the foot, all those patients who gave a history of dermatitis starting in this area were patch tested with the suspected shoe allergen in the last year of the period covered in this study. Thus were found a number of cases in which both dermato-

phytosis and contact dermatitis were apparently active simultaneously in the same patient. Confusion in diagnosis was even greater when typical dermatophytids of the hands were present.

There was no apparent correlation between the length of time the shoes were worn and the appearance of the dermatitis. In some cases the dermatitis would develop some weeks after the wearing of a new pair of shoes; in others there was

Fig. 2.—*A*, extensive contact dermatitis involving the soles and resembling a dermatophytosis. *B*, lesions of the hands resembling a dermatophytid.

no history of recent purchase of shoes. Some patients, known to be sensitive, would be able to wear a new shoe containing the offending agent for months before developing the dermatitis, whereas other such patients would develop dermatitis within 24 hours. We did note in the histories an increase in the appearance or recurrence of the dermatitis in periods of hot weather when there was excessive sweating of the feet. Surprisingly, several patients developed explosive exacerbations of their eruption in cold weather, but they gave a history of wearing shoes unprotected by overshoes in rain or snow.

Review of the Literature.—A review of the literature since 1925, undertaken at this point, shows an interesting evolution in causes advanced for contact dermatitis due to shoes. In the last half of the third decade reports were essentially of shoe dye poisoning with systemic manifestations, although several reports of dermatitis due to aniline shoe dyes can be found. These reports of dermatitis due to shoe dyes became more common in the early 1930's. At about this time reports of dermatitis due to shoe leather began to appear and became more common in the late 1930's.*

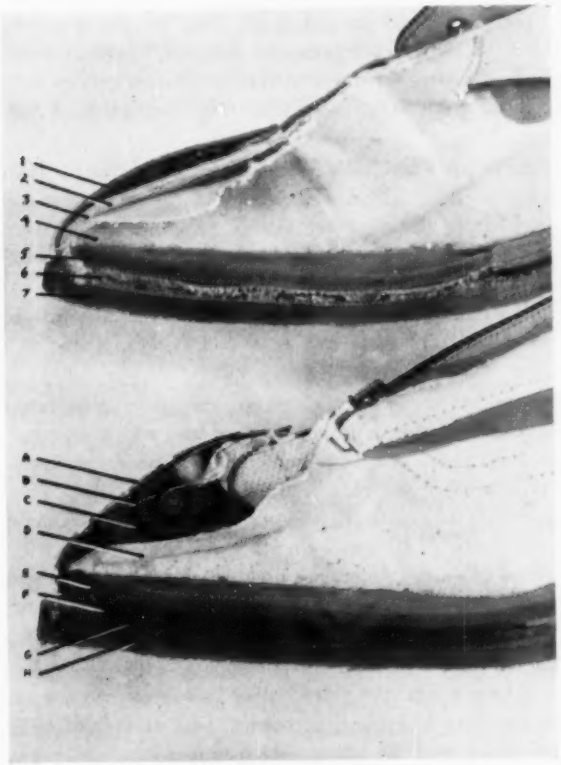

Fig. 3.—Top, front half of shoe with a flannel box toe: (*1*) outside leather; (*2*) waterproofed paper; (*3*) flannel box toe; (*4*) cotton drill lining; (*5*) leather inner sole; (*6*) midsole of ground cork-rubber mixture; (*7*) leather outer sole.

Bottom, front half of shoe with a thermoplastic box toe: (*A*) outside leather; (*B*) coarse cotton lining (waterproofed paper is visible against outside leather); (*C*) thermoplastic box toe; (*D*) cotton drill lining; (*E*) leather inner sole (*F*) rubber asphalt filler; (*G*) sheet of reclaimed rubber; (*H*) leather outer sole.

The various substances involved in the tanning, finishing and dyeing of leather were incriminated.

In the 1940's, starting with Marcussen's work,† one finds discussions of dermatitis due to various resins, fillers, plastics and rubber adhesives, with less importance

† References 8-13.

* References 2-7.

attributed to the dyes and leathers as a source of contact dermatitis. Gaul and Underwood [14] in 1949 showed clearly the shift in emphasis from leather and dye to other materials in shoes as the source of contact dermatitis. They were also suspicious of the adhesive materials in shoes as being one of the primary causes of contact dermatitis. Blank and Miller [15] in 1952 emphasized the importance of rubber adhesives in women's shoes in their series of cases of contact dermatitis of the feet.

The Structure of Shoes.—The structure and composition of a shoe varies with the manufacturer, the style, and the times. A variety of materials goes into the manufacture of each individual portion of the shoe, and these materials vary from year to year as new substances are perfected, attaining identical results at less cost. However, the basic composition and structure of all men's shoes are rather similar regardless of style or trademark. Following is a description of the average shoe (Fig. 3).

When the shoe is cut lengthwise, it is seen that the forward half consists of an upper and a lower portion. The lower portion of the shoe (the sole) consists of an inner sole, a midsole and an outer sole. The inner sole is usually of leather attached to the midsole by a rubber cement. The midsole consists either of a layer of fabric upon which is cemented a layer of a ground cork-rubber mixture or of a sheet of reclaimed rubber with a rubber-asphalt filler inserted between this rubber sheet and the inner sole. The outer sole may be of leather, plastic, or rubber, singly or in sheets.

The upper portion of the shoe (the toecap) consists of four layers: the outside leather, a sheet of waterproofed paper, the box toe, and the lining. The outside leather is either sewn to the sole or joined to it by a waterproof welt. The waterproofed paper is inserted if the outer leather has perforations. The box toe is of three general types: thermoplastic, flannel impregnated with pyroxylin, or buckram. The lining, usually made of cotton cloth, also known as cotton drill, may be dyed or may be of natural color, the commoner practice. Usually it is impregnated with a fungicide to prevent mildew. Some shoes have a leather rather than a cotton drill lining. Some shoes, like the moccasin, have neither box toe nor lining.

The back half of the shoe consists of an upper portion and a heel. The upper portion consists of four layers: the outer leather; a burlap material with a felt backing cemented to the outside leather, a counter, made either of stiff leather or of impregnated stiff paper, and the lining, which is usually a softer grade of leather. The heel consists of several layers of leather, the leather lining, which is continuous with the leather inner sole of the forward half of the shoe, and a heel pad, usually a very thin sheet of paper, cemented to the lining by rubber cement.

The middle third of the sole, connecting the forward half with the heel, has the same structure as the sole but with a shank of wood or metal replacing the softer, more pliable midsole.

This basic shoe structure is also seen in the Oxford type of shoe worn by women and children. Women's shoes of the dress type are of very much lighter construction. The upper may be a mere skeleton, consisting of several straps of leather, simulated leather, or fabric lined with leather or fabric; or it may be a toeless shoe or the sling type without a back section. The sole may consist of several thin sheets of leather with a thin shank to act as a stiffener in the middle third. There are fewer materials

used in the construction of such a light shoe and there is also much less contact with the foot as well as greater opportunity for the foot to remain dry through the evaporation of perspiration. All these factors decrease the incidence of contact dermatitis from this light type of shoe. The shoes of infants usually consist of a leather upper with no lining and a buckram box toe. Here again the types of materials as well as the number are much fewer than in the adult shoe, thus decreasing the opportunity for development of contact dermatitis.

REEVALUATION OF CASES

The irregularity of patch test results as compared with the fairly constant clinical picture made us undertake a more complete study of the subject of contact dermatitis due to shoes. We thought that there might be a basic sensitizing agent or group of agents.

In cutting open shoes for patch testing we had noted the effect of wear and sweating on the lining. Cotton linings were torn and discolored, and it was obvious that testing with such lining could well give false results because of the leeching out into the lining of substances from other parts of the shoe. In studying the records we noted that this possibility had been neglected in testing shoe-sensitive persons. We therefore decided to reinvestigate all the previously hospitalized cases of shoe dermatitis, keeping this possibility in mind.

At this point we recalled all patients hospitalized during the period 1947-1951 with a diagnosis of dermatitis venenata due to shoes. There were 34 patients who had been hospitalized 42 times. We were able to reexamine and reevaluate 31 patients of this group of 34.

We are dealing in this paper specifically with the problem of dermatitis due to shoes. Naturally, a certain number of individuals will develop a dermatitis due to the dyes, etc., found in socks, and the socks did come into question when a patient with a dermatitis of the foot was first seen. However, both the history and the substitution of white cotton socks for colored socks of various materials usually eliminated the sock as a causative factor in the dermatitis. In fact, many of the patients had already made the change to white cotton socks before being seen by us. We have reevaluated only those patients who, in our estimation, presented a contact dermatitis due to shoes.

In reviewing the charts of all cases of dermatitis or dermatophytosis of the feet for the same period we found 20 more cases which in retrospect might have been examples of contact dermatitis due to shoes although not diagnosed as such at the time of hospitalization. We also recalled these 20 patients but without success.

Although of little statistical significance, it appears that contact dermatitis due to shoes (as originally diagnosed) was much more chronic and disabling to the patient, thus explaining the response of this group to our letter. The 20 patients originally diagnosed as having miscellaneous dermatoses arising on the feet apparently were much less troubled by their condition and therefore did not reply. There may be other reasons for the difference in response to our letter between these two groups, but the fact that most of those cases due to shoes still showed evidence of dermatitis when reexamined seems to favor this interpretation. This only serves to emphasize further the chronicity of shoe dermatitis, the extent of disability, and the economic problem it can create for the patient.

Since in the majority of patients the eruption was confined to the dorsal surfaces of the toes with extension to the back of the foot, we suspected that some specific substance in the toecap might be the offending agent.

Pilot Study.—The first three patients were retested with used materials taken from the toecaps of their own worn shoes. We sectioned the shoe and patch tested each patient with the upper leather, both inner and outer aspects, the cotton drill lining, and the box toe. (The box toe in each of these cases was of the thermoplastic type.) Two patients gave positive reactions to the box toe, cotton drill, and the inner aspect of the leather; one patient gave positive reactions to the box toe and cotton drill but negative reactions to both sides of the leather. We then attempted to determine the identity of the substance or substances causing the positive reactions.

After consultation with a shoe manufacturer we learned that the manufacturing process where the thermoplastic box toe is used might explain some of our results. The thermoplastic material is run over a hot roller before being inserted into the shoe and is then molded into the proper shape in the shoe while still warm. This material is adhesive when warm so that it adheres to the leather and impregnates the cotton lining. Thus, when patch testing with materials removed from the shoes we might have been patch testing with the same thermoplastic material, even though we were attempting to test three distinct substances.

The shoe manufacturer supplied us with samples of new materials used in the toe cap. Several of our patients had been wearing shoes manufactured by his concern. Although we could have no assurance that these materials were identical with those used in the shoes of our patients, we were told there had been no change in the manufacturing process in the last few years and the materials supplied us were essentially of the same nature as those used in the patch tests on the first patients.

The same three patients were then retested with the new thermoplastic material, the cotton drill, and leather. We found in each instance positive reactions to the thermoplastic material and negative reactions to leather and cotton drill.

In order to check the possibility that the continued exposure of the inside of the shoe to perspiration might have the effect of leeching out some of the substances from the thermoplastic material into the cotton drill lining, we shredded some thermoplastic material and allowed it to stand in normal saline solution for one week. This suspension was then filtered, and the same patients were tested with the filtrate. Positive patch test reactions in all three patients seemed to confirm the probability that shoes worn for any length of time would have present on the lining some materials from the box toe merely through the solvent action of the sweat.

The method of shoe manufacturing and the leeching effect of perspiration and moisture could thus easily explain the irregular patch testing results obtained with materials taken from old shoes. Leather and lining, which were basically not at fault, could give positive reactions in an irregular fashion, depending on whether or not the portion of shoe selected for testing had become contaminated by materials from the thermoplastic box toe.

The sensitization to thermoplastic box toe materials could also develop through direct contact with the box toe rather than through contact with the contaminated

lining. The toe cap lining is frequently worn away completely in old shoes, and the sock-encased foot is in immediate contact with the box toe. There is fairly massive contact with the box toe in this fashion.

It is true that the contact with the box toe is always through the intermediary of the sock. However, just as the perspiration passes through the toe cap lining to reach the box toe and leech out any sensitizing materials, it can also pass through the sock and then go on to reach the box toe. In the case in which the toe cap lining is torn, the perspiration passing through the sock can even more easily come in contact with the sensitizing materials. The sock therefore does not act as a complete barrier but can prolong the time before contact with sensitizing materials will occur. In those cases in which there is insufficient perspiration to moisten the sock there will probably be no leeching effect and no sensitization.

Our small pilot study seemed to implicate the box toe as the offending agent in these cases of contact dermatitis. The waterproofed paper, the fourth element in the toe cap, is an inconstant factor. A coarse undyed cotton fabric is found in its place in shoes with nonperforated toe caps and this cotton can be eliminated as a sensitizer, since it is basically similar to the cotton lining. The continued presence of the dermatitis even when the patient was wearing shoes without the waterproofed paper permitted us to eliminate it as the sensitizer.

The two important types of box toes in men's shoes are made either of thermoplastic material or of flannel impregnated with pyroxylin. We tested the pilot patients with new flannel (all flannel tests in this study were made with the impregnated material) and obtained negative reactions. We then cut open all the shoes of these patients and found only thermoplastic box toes. We thus satisfied ourselves that the thermoplastic material was the specific sensitizer and the cause of the dermatitis in these cases.

There are comparatively few cases of shoe dermatitis, considering the millions of shoes worn, and we assume that the leather, cotton drill, and box toe are not primary irritants. However, to eliminate the possibility of these acting as irritants when employed under patch testing conditions we tested 100 subjects selected at random. There were no positive reactions to leather, cotton drill, or flannel. There were two positive reactions to the thermoplastic material. One was in a person who suffered from a dermatitis of the feet always diagnosed as dermatophytosis. However, the dermatitis was eventually controlled by eliminating thermoplastic material from his shoes, indicating that he was truly sensitive to this material. The second positive test was in a subject who had no foot lesions but was found to have positive patch test reactions to various rubbers. In our later discussion on the relationship of thermoplastic material and rubber it will be seen that this can be regarded as a true sensitization rather than an irritative reaction. We therefore feel that these materials used in patch tests were not acting as irritants.

Patch Testing Recalled Cases.—Recalled patients were tested with the new thermoplastic material, cotton drill lining, leather, and flannel. Standard patch testing techniques were employed, with the patches applied on the upper back and the reactions read in 48 hours. All patients with positive reactions to thermoplastic material were also tested with a series of rubbers. These rubbers were ground red rubber inner tube, GRS Buna synthetic rubber, reclaimed rubber which came in sheet form, ground girdle rubber, rubber midsole and cork-rubber mixture.

Table 1 shows the results of these various patch tests. There is an indication for each case as to whether the original diagnosis was made on clinical grounds or by patch test confirmation. There is a single column labeled "rubbers." If the patient reacted to any one type of rubber, a positive reaction is indicated in this column.

Eighteen patients had been diagnosed on clinical grounds. Nine of these now had positive reactions to thermoplastic material and negative reactions to leather, cotton drill, and flannel. The remaining nine showed completely negative reactions

TABLE 1.—*Summary of Patch Test Data on Recalled Patients*

Case No.	Basis for Original Diagnosis	Thermoplastic	Cotton Drill	Leather	Flannel	Rubbers
1	Clinical	+	—	—	—	+ (3)
2	Patch tests	+	—	—	—	+ (4)
3	Clinical	+	—	—	—	—
4	Clinical	+	—	—	—	+ (5)
5	Clinical	—	—	—	—	0
6	Patch tests	+	—	—	—	+ (5)
7	Clinical	—	—	—	—	0
8	Patch tests	—	—	—	—	—
9	Patch tests	—	—	—	—	—
10	Clinical	+	—	—	—	+ (2)
11	Clinical	—	—	—	—	0
12	Clinical	+	—	—	—	+ (1)
13	Clinical	+	—	—	—	+ (4)
14	Patch tests	+	—	—	—	+ (5)
15	Clinical	—	—	—	—	0
16	Patch tests	+	—	—	—	+ (3)
17	Patch tests	—	—	—	—	+ (5)
18	Clinical	+	—	—	—	+ (2)
19	Patch tests	+	—	—	—	+ (1)
20	Patch tests	+	—	—	—	+ (2)
21	Patch tests	+	—	—	—	+ (1)
22	Clinical	—	—	—	—	0
23	Patch tests	+	—	—	—	+ (6)
24	Clinical	—	—	—	—	0
25	Clinical	+	—	—	—	+ (1)
26	Clinical	—	—	—	—	0
27	Clinical	—	—	—	—	0
28	Clinical	—	—	—	—	0
29	Patch tests	+	—	—	—	—
30	Clinical	+	—	—	—	+ (5)
31	Patch tests	—	—	—	—	0

Explanation of symbols: —, negative reactions; +, positive reactions; 0, not tested. Numbers in parentheses in last column indicate the number of rubbers to which the patient reacted.

to all these substances. Thirteen patients had the original diagnosis based on positive reactions to leather, lining, heel pad, rubber cement, etc. Nine of these now had positive reactions to thermoplastic material and negative reactions to leather, cotton drill, and flannel. The remaining four patients (Cases 8, 9, 17, 31) had negative reactions to all these substances. Sixteen out of the 18 who had positive reactions to thermoplastic material also had positive reactions to at least one of the rubbers.

Late in our investigation we found one patient (Case 17) with multiple positive rubber reactions but a negative reaction to thermoplastic material. This patient had a contact dermatitis of the hands due to handling rubber cable and also had a dermatitis of the heels on his original admission.

Patch Testing New Cases.—We observed 18 new cases during the period 1952-1953 while we were investigating our original series. Similar studies were made and the results are shown in Table 2. One patient (Case 49) had a dermatitis of the dorsum of the feet due to a leatherette lining in sandals and he gave negative reactions to rubber, thermoplastic material, and the other test materials. The remaining 17 cases had positive reactions to thermoplastic material and one or more rubbers, and negative reactions to leather, flannel, and cotton drill. One of these patients (Case 42) had a dermatitis of the sole due to rubber midsole with no lesions on the backs of the feet. Another patient (Case 39) had a dermatitis of the hands in addition to an eruption on the feet, but he also had to handle rubber in his work. Thus most of the cases seen in the last two years have fallen into the group with a dermatitis of the dorsum of the feet and positive reactions to thermoplastic material and rubber.

TABLE 2.—*Summary of Patch Test Data on New Patients*

Case No.	Thermoplastic	Cotton Drill	Leather	Flannel	Rubbers
32	+	—	—	—	+ (6)
33	+	—	—	—	+ (2)
34	+	—	—	—	+ (6)
35	+	—	—	—	+ (1)
36	+	—	—	—	+ (2)
37	+	—	—	—	+ (2)
38	+	—	—	—	+ (2)
39	+	—	—	—	+ (2)
40	+	—	—	—	+ (1)
41	+	—	—	—	+ (4)
42	+	—	—	—	+ (3)
43	+	—	—	—	+ (3)
44	+	—	—	—	+ (4)
45	+	—	—	—	+ (4)
46	+	—	—	—	+ (5)
47	+	—	—	—	+ (2)
48	+	—	—	—	+ (3)
49	—	—	—	—	—

Explanation of symbols: —, negative reactions; +, positive reactions. Numbers in parentheses in last column indicate the number of different rubbers to which the patient reacted.

Patch Testing with Thermoplastic Ingredients.—The company producing the thermoplastic material described the manufacturing process and supplied us with samples of the ingredients. Carded felt (wool or cotton) is pretreated with synthetic rubber and then shredded. A mixture of ground red rubber inner tube, Parawax (paraffin), Piccolastic (styrene), Vinsol (a refined rosin), Penbro (a modified turpentine resin), Penbro 70 (limed pembro), rosin and asphalt is heated to 360° F. and mixed with the rubberized felt. Polyethylene glycol (Carbowax) 6000 is then added, and the mixture is cooled and rolled into sheets. Prior to 1940 crude rubber was used in the manufacture of this box toe, but with the rising costs and scarcity of rubber during World War II various types of scrap rubber were substituted.

Fourteen patients who had positive reactions to the thermoplastic material were tested with all the basic ingredients. Table 3 shows the results of these tests. Ten patients had positive reactions to ground red rubber tube; of the four nonreactors

one had a positive reaction to Buna rubber. Thus 11 out of 14 patients reacted to at least one of the rubbers. Four out of these 11 also reacted to other substances: 1 to resins (Case 34); 1 to resins and asphalt (Case 16); 1 to asphalt (Case 10); 1 to styrene (Case 41). Among the three patients who did not react to rubber were found one (Case 30) who reacted to a group of resins and two (Cases 3 and 29) who reacted to none of the thermoplastic ingredients.

Discussion of Patch Test Results.—It became obvious from the sampling shown in Table 3 that rubber was the primary cause of the contact dermatitis we were studying. This was further demonstrated by the positive reactions to some form of rubber in every one of the patients with a positive thermoplastic reaction except Cases 3 and 29. However, if we wish to incriminate rubber, we have the problem of explaining the results in Cases 3 and 29. The results in Case 30, who reacted to thermoplastic material and a group of rosins but not to the rubber, must also be explained.

TABLE 3.—*Results of Patch Tests With Primary Ingredients of Thermoplastic Material*

Case No.	Ground Red Rubber	Parawax	Piccolastic	Vinsol	Penbro	Penbro-70	Rosin	Carbowax	Asphalt	Felt	GRS	Felt GRS
2	+	—	—	—	—	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—	—	—	—	—	—
6	+	—	—	—	—	—	—	—	—	—	+	—
10	+	—	—	—	—	—	—	—	+	—	—	—
13	+	—	—	—	—	—	—	—	—	—	—	—
14	+	—	—	—	—	—	—	—	—	—	—	—
16	+	—	—	+	—	+	+	—	+	—	+	+
20	+	—	—	—	—	—	—	—	—	—	—	—
29	—	—	—	—	—	—	—	—	—	—	—	—
30	—	—	—	+	+	+	+	—	—	—	—	—
32	+	—	—	—	—	—	—	—	—	—	—	—
34	+	—	—	+	—	—	+	—	—	—	—	—
41	—	—	+	—	—	—	—	—	—	—	+	+
45	+	—	—	—	—	—	—	—	—	—	+	—

Explanation of symbols and terms: +, positive reactions; —, negative reactions. Parawax is paraffin; Piccolastic, styrene; Vinsol, refined rosin; Penbro, modified turpentine rosin; Penbro 70, limed rosin; GRS, synthetic Buna rubber; felt GRS, felt-rubber mixture.

We can still consider the positive thermoplastic reaction an example of rubber sensitivity if we wish, but we must understand when we use these words that we are not talking about sensitivity to the crude rubber as such. We are talking rather about sensitivity to the various accelerators and antioxidants employed in the rubber manufacturing process.[16]

The subject of sensitivity to accelerators and antioxidants has been well studied. There are a large number of these, some being used more commonly than others and some having a much higher sensitizing potential than others. Where rubber is used in direct contact with the skin in industry, it has been found necessary to forego completely the use of some of these substances because of their high rate of sensitization.

The problem of determining the specific antioxidant or accelerator in the rubber employed in the toe cap and midsole is of little clinical value. There is no need for a crude or pure rubber in the manufacture of the toe cap and midsole. Every type of scrap rubber imaginable can be used as long as the proper adhesive and elastic

qualities can be imparted to the finished product. There is no way of knowing what mixture of antioxidants and accelerators is present in the rubber employed because of the various methods of originally processing the crude rubber. We made no attempt to determine the specific chemical nature of the sensitizer in the rubber. Even if we could determine a single chemical as being the sensitizer in any one case, there is no way of it being economically feasible to manufacture a box toe of thermoplastic material in which the sensitizing agent has been omitted.

We can at this point possibly explain those examples of positive reactions to thermoplastic material in patients who had negative reactions to its primary ingredients and to all rubbers. The patient might have been sensitized to a specific antioxidant or accelerator. This might be present in his own shoes and the thermoplastic material we were using in our tests but not in the scrap rubbers we were testing (Cases 3 and 29). Case 30 did not react to the primary rubber materials but did react to other types of rubber and thus seems to illustrate this explanation for the apparent inconsistencies in the reactions to thermoplastic material and the various rubbers.

The same type of explanation could be applied to the positive reactions to rubber and the negative reaction to thermoplastic material in Case 17. It is possible that had we tested the 10 remaining patients with negative thermoplastic reactions to the various rubbers we might have obtained more cases similar to Case 17. We might thus have indirectly obtained patch test proof of sensitivity to thermoplastic box toe as the cause of a dermatitis which clinically was apparently due to shoes.

The positive patch test reactions to multiple substances including rubber (Table 3) is not too surprising when one considers the constant exposure to these foreign materials. It is fairly well accepted that a skin injured by a dermatitis can more easily become sensitized. Case 34 had an intermittent dermatitis from 1949 to 1952, necessitating hospitalization twice. Case 16 had a dermatitis of the feet continuously for one year. Case 10 had a seven year history of an intermittent dermatophytosis and a continuous dermatitis for four months. Case 41 had a dermatitis intermittently for eight years and continuously for two months prior to hospitalization. We probably have examples here of a "widening of the base" in allergic contact dermatitis.

There were 10 patients (Table 1) with negative thermoplastic reactions whom we did not test for rubber sensitivity. One assumption is that these patients were sensitive to shoe substances other than thermoplastic material. The stock materials we were using in our tests were possibly different from the shoe materials to which they were actually sensitized. An example of this would be Case 31, in which positive patch test reaction to leather from his own shoe was obtained during his original hospitalization. Another assumption could be definite loss of sensitivity. Cases 8 and 9 originally had a dermatitis of the heels due to rubber cement but had negative reactions to various rubbers on retesting, as well as to thermoplastic material; (these two cases although negative to thermoplastic materials, were retested with rubbers because of the original proved rubber cement dermatitis). They have had no trouble with their feet for several years, although they are taking no precautions against rubber cement on heel pads. However, it is possible that the specific antioxidant or accelerator responsible for their rubber cement dermatitis has been abandoned and

is no longer found in the newer rubber cements and rubbers. This would then be an example of not testing with the specific sensitizer rather than a loss of sensitivity. The last possible explanation for the negative tests is that the cases originally diagnosed as contact dermatitis were misdiagnosed.

In summary, out of 31 cases of dermatitis probably due to shoes, sensitivity to thermoplastic material was demonstrated in 18, and of these, 16 were also sensitive to various rubbers. A 19th case showed sensitivity to rubbers but not to thermoplastic material. In addition, 18 new cases of shoe dermatitis were diagnosed, and, of these, 17 were sensitive to thermoplastic material and rubber.

CURE BY ELIMINATION OF THERMOPLASTIC BOX TOE

Our patch test results all pointed to the thermoplastic box toe as being the primary cause of the dermatitis when it originates or is localized on the back of the toes. Our most important test in implicating thermoplastic material was our ability to cure the dermatitis by eliminating the thermoplastic box toe. Ordinary, commercially available shoes were purchased by the patients. These shoes were certified by both the retailer and the manufacturer to have been made with the flannel box toe.

Twelve patients purchased such shoes. Nine of these patients (Cases 10, 13, 16, 18, 19, 23, 38, 45, 48) have had no recurrence of their dermatitis since wearing these shoes, a minimum period of one and a half years for each patient. One patient (Case 37) remained clear for four months and then had a recurrence when he began to wear shoes of the type he had previously worn. One patient (Case 14) remained clear for six months and then developed a recurrence when he once again began to wear his usual brand of shoes. The 12th patient (Case 4) has had no recurrence of the dermatitis of the dorsum of his feet for one and a half years but has had several outbreaks of a dermatitis of the soles. Dermatophytes have been demonstrated in skin scrapings of this area, and we have diagnosed the plantar dermatitis as a dermatophytosis. The plantar dermatitis has cleared each time without changing shoes, thus eliminating the possible diagnosis of a dermatitis due to a rubber midsole.

The flannel box toe is found only in the higher-priced shoes, in our experience. The difference in cost explains the small number of patients who submitted to a use test. Cases 37 and 14 are examples of the difficulty we had in persuading patients to take our advice. They had the benefit of a cure while wearing shoes with the flannel box toe, and even this proof did not prevent them from wearing the less expensive shoe with the thermoplastic box toe.

One case of heel dermatitis (Case 17) was easily cured by elimination of the heel pad with its rubber cement. Another case (Case 42) with a sole dermatitis was cured by removal of the rubber midsole and substitution of a felt in a new pair of shoes.

CONCLUSIONS

We have thus come to the conclusion that most of our cases of contact dermatitis due to shoes are examples of allergic contact dermatitis due to rubber, it being understood that antioxidants and accelerators are actually the sensitizers in rubber. Even more important is that the majority of the cases appear to have the clinical dermatitis precipitated by contact with the thermoplastic box toe which contains rubber. Those patients with thermoplastic sensitivity are easily cured by the use of shoes with a flannel box toe.

It is true that rubber cements are found in various parts of the shoe and rubber is always present in the midsole. In actual practice these are rarely the causative agents of the dermatitis as compared with the thermoplastic box toe. Variation in the amount of pedal sweat, shoes becoming wet in rain and snow, variable rate of wear of different parts of the shoe because of anatomic structure of the foot, frequent changing of shoes, individual sensitivity—all these factors explain why one patient develops a dermatitis on the dorsum of the feet, another on the soles, and a third on the heels.

From a practical point of view our work-up and treatment of dermatitis due to shoes has become greatly simplified. When we suspect a patient of having a contact dermatitis due to shoes we routinely test with thermoplastic material and a group of rubbers. If any of these is positive, we eliminate the thermoplastic box toe both as a curative and prophylactic measure and either the rubber midsole or the heel pad if the starting point of the dermatitis appears to incriminate either of these. If the reactions to the stock thermoplastic material and rubbers are negative, then we find it necessary to investigate the patient's own shoes. This procedure is much more difficult and usually less productive of results than the use of the stock patch tests.

SUMMARY

A group of hospitalized patients with dermatitis of the feet due to shoes is studied.

Thermoplastic box toe is shown to be the factor in the majority of the cases, and rubber is the essential ingredient in thermoplastic material that is the actual offender. It is pointed out that the antioxidants and accelerators in rubber are actually the basic sensitizers.

Cure of the dermatitis by substitution of a shoe with a flannel box toe for the thermoplastic box toe is easily obtained.

Diagnosis of shoe dermatitis has been greatly simplified since we have learned that thermoplastic material is the most common sensitizer.

REFERENCES

1. Kierland, R. R.: Problems of Military Dermatology, A. M. A. Arch. Dermat. & Syph. **68**:54, 1953.

2. Suchier, R.: Acute Dermatitis from Shoe Dyes, München. med. Wchnschr. **75**:570, 1928.

3. Ramond, L.: Dermatitis Provoked by Aniline Shoe Dye, Presse méd. **39**:763, 1931.

4. Callan, T., and Strafford, N.: Examination of Dyed Leather in Cases of Alleged Dermatitis, Analyst **56**:625, 1931.

5. Lewis, G. M.: Dermatitis Venenata Due to Shoe Leather: 2 Cases, Arch. Dermat. & Syph. **24**:597, 1931.

6. Anderson, N. P., and Ayres, S. J.: Dermatitis Venenata Due to Shoe Leather: Case, J. A. M. A. **99**:25, 1932.

7. Lanzenberg, P.: Artificial Eruption of Feet Provoked by Dyed Shoe Leather, Bull. Soc. franç. dermat. et syph. (Réunion dermat., Strasbourg) **39**:1464, 1932.

8. Marcussen, P. V.: Footwear as Cause of Eczema of Feet, Nord. med. (Hospitalstid) **11**:2507, 1941.

9. Marcussen, P. V.: Rubber Footwear as Cause of Foot Eczema, Acta dermat.-venereol. **23**:331, 1942.

10. Robins, A.: Allergic Dermatitis from Footwear, South African M. J. **17**:345, 1943.

11. Dolce, F. A.: Shoe Dermatitis Among Soldiers, Mil. Surgeon **95**:505, 1944.

12. Shaw, C.: Dermatitis Venenata Due to Shoes, Arch. Dermat. & Syph. **49**:191, 1944.

13. Jordan, J. W.: Contact Dermatitis Due to Synthetic Resins in Shoe Linings, Arch. Dermat. & Syph. **62**:671, 1950.

14. Gaul, L. E., and Underwood, G. B.: Primary Irritants and Sensitizers Used in Fabrication of Footwear, Arch. Dermat. & Syph. **60**:649, 1949.

15. Blank, I. H., and Miller, O. G.: A Study of Rubber Adhesives in Shoes as the Cause of Dermatitis of the Feet, J. A. M. A. **149**:1371, 1952.

16. Schwartz, L.; Tulipan, L., and Peck, S.: Occupational Diseases of the Skin, Ed. 2, Philadelphia, Lea & Febiger, 1947.

17. Gaul, L. E., and Underwood, G. B.: Failure of Modern Footwear to Meet Body Requirements for Psychic and Thermal Sweating, Arch. Dermat. & Syph. **62**:33, 1950.

INCONTINENTIA PIGMENTI IN JAPAN

Introduction of Twenty-One Observed Cases

KANEHIKO KITAMURA, M.D.
RYOICHI FUKUSHIRO, M.D.
AND
TETSU MIYABAYASHI, M.D.
TOKYO, JAPAN

AN INCREASED interest in incontinentia pigmenti is indicated by the recent articles of Carney,[1] Epstein and others,[2] Haber,[3] and Findlay,[4] who regard this disease not merely as a skin disease but preferably as a widespread syndrome comprising various congenital disorders.

In Japan, Kitamura and Chan[6] described, in 1938, a baby girl showing the characteristic pigmented patterns of incontinentia pigmenti as the first Japanese case of this disease. Since then, 21 cases of incontinentia pigmenti have been observed in this country. However, as most of them * were reported in Japanese medical journals during the recent war, they are unknown to world dermatologists, with the exception of the first case of Kitamura and Chan, which at that time was abstracted in *Dermatologische Wochenschrift*.[7] So the relative frequency of this disease among the Japanese people, which is now presumed from the above-mentioned number of the observed cases, is not yet recognized universally.

In this paper, the hitherto observed 21 Japanese cases—our own 8 plus 13 other cases of incontinentia pigmenti—which are presented briefly in the accompanying Table, are summarized for the further consideration of this disease.

A familial incidence of incontinentia pigmenti, as has been reported by Bardach [15] and Nägeli,[10] was demonstrated in three cases. In Case 10, the father has a small, very obscure lesion on the right breast, resembling that of the patient. This case is also noteworthy because of double consanguinity existing in the family. The grandmother on the paternal side is a cousin of her husband, the grandfather on this side, as well as of the maternal grandmother who is the sister of the latter, therefore the parents are also cousins. In Cases 11 and 12, the girls are sisters, and their mother probably has similar, although atrophic, lesions on her legs. In Case 15, one second cousin on the maternal side, female, has a large port-wine mark on the right half of the face. Besides, the father, his three brothers, and especially five sisters have similarly many lentigines, and of the sisters there is a pair of identical twins. Some disorders other than the skin lesions also have been found in the families of these cases. In Case 10, one maternal uncle and aunt are psychotic. In Cases 11 and 12,

From the Department of Dermatology, Faculty of Medicine, University of Tokyo.

* References 8-17.

the mother of the patients has lost two children by miscarriage and is now psychotic; a 4-year-old sister of these patients has epilepsy. In Case 15, one paternal 8-year-old cousin, a girl, is backward in speaking. In Case 21, one paternal aunt is weak-minded.

Hitherto Observed Japanese Cases of Incontinentia Pigmenti

Case No.	Publication or Examination, Date and Author	Sex	Age at Examination	Skin Lesions at Present*	Onset of Skin Lesions	
					Pigmentation	Inflammatory Changes
1	1938 Kitamura and Chan [6]	F	93 days	PSVsVr	Present at birth	Erythemas, wheals, and vesicles, shortly after birth
2	1939 Kitamura [7]	F	3 yr.	PE	At the age of 3	Inflammatory redness, simultaneously with pigmentation
3†	1943 Yokoyama and Katayama [9]	F	21 days	PEErC	Present at birth	Erythemas, within 1 wk. after birth
4	1946 Ito‡	F	11 mo.	P	After inflammatory eruptions	Erythematous eruptions with intermittent fever, 10 days after birth
5	1946 Ito‡	F	7 mo.	P	After inflammatory eruptions	Erythematous eruptions, present at birth
6	1946 Ito§	F	26 yr.	P	After inflammatory eruptions	Varicelliform eruptions, 100 days after birth
7†	1950 Minami [14]	F	13 mo.	P	After inflammatory eruptions	Pustular eruptions, shortly after birth
8	1951 Kitamura and Fukushiro [15]	F	8 mo.	PVs	Present at birth	Vesicles, in succession to pigmentation
9	1951 Kitamura and Fukushiro [15]	F	3 mo.	P	Present at birth	Eczematous eruptions, in succession to pigmentation
10	1951 Kitamura and Fukushiro [15]	F	15 mo.	P	Present at birth	Vesicular eruptions, accompanied by pigmentation, present at birth
11	1951 Kitamura and Fukushiro [15]	F	5 mo.	PVsCVr	Present at birth	Pustular eruptions, in succession to pigmentation
12	1951 Kitamura and Fukushiro [15]	F	11 yr.	P	Present at birth	Inflammatory eruptions not recalled
13	1952 Higuchi and others [16]	F	8 mo.	PEVr	After inflammatory eruptions	Vesicles, 10 days after birth
14	1952 Higuchi and others [16]	F	13 mo.	P	After inflammatory eruptions	Vesicles, 2-3 days after birth
15	1952 Higuchi and others [16]	F	8 mo.	P	After inflammatory eruptions	Vesicles, soon after birth
16‖	1952 Ito [17]	F	22 yr.	Dp	Depigmented spots and streaks appeared in early childhood	No description of inflammatory changes
17	1952 Kitamura, Fukushiro, and Miyabayashi ¶	F	14 mo.	PEVsVr	After inflammatory eruptions	Bullous eruptions, 20 days after birth
18	1952 Miura ¶	F	17 mo.	PE	After inflammatory eruptions	Vesicles, 10 days after birth
19	1952 Watanabe ¶	F	10 mo.	PEVr	After inflammatory eruptions	Vesicles and erythematous areas appeared 30 min. after delivery
20	1952 Kawamura ¶	F	8 mo.	PEErVr	After inflammatory eruptions	Vesicles, 10 days after birth
21	1952 Sakurane ¶	F	81 days	PEVs	Present at birth	Vesicles and erosions, 4 days after birth

* P, pigmentation; E, erythema; Er, erosion; Vs, vesicles; Vr, verruca; C, crust; Dp, depigmentation.

† Dr. Yokoyama told us personally that after Case 3 he saw one more case. Minami stated in his paper on Case 7 that he also had seen formerly one additional case.

‡ References 10-13. Cases 4 and 5 were first reported in 1934 by Saito,[10] a pupil of Ito, both as nevus systematicus, afterwards identified by Ito with incontinentia pigmenti.

§ References 11-13.

‖ Case 16 was named incontinentia pigmenti achromians by Ito, because of the depigmented lesions; see text.

¶ Cases 17, 18, and 20 are not yet published elsewhere. Cases 19 and 21 will appear soon in *Japanese Journal of Dermatology and Venereology*, the former as a report at a meeting and the latter as an original article. Cases 18 to 21 were offered for this publication by Drs. Miura, Watanabe, Kawamura, and Sakurane.

A strong sex predominance in incontinentia pigmenti, that is, the partiality of the disease to females, as shown in Carney's review of the literature,[1] is fully affirmed in these 21 Japanese cases, in which all the patients are females. In the 37 cases of Carney's review there are 33 females and 4 males.

The characteristic pigmented patterns of incontinentia pigmenti were present at birth in eight cases. In most of them inflammatory changes occurred thereafter on the pigmented skin, while in another 11 cases erythemas and/or vesicular eruptions were present at birth or appeared prior to the pigmentation. In Case 2, in which the diagnosis of incontinentia pigmenti was made with some hesitation, the pigmentation appeared accompanied by inflammatory redness late, at the age of 3 years. In Case

Fig. 1 (Case 10).—Pigmented patterns consisting of waving transverse streaks, whorls, and small patches. On the median line pigment patches are longitudinally arranged.

Fig. 2 (Case 10).—Pigmentary network composed of concave demarcated patches, showing variously sized round meshes containing normal skin.

12, the 11-year-old girl cannot recall having had any inflammatory eruptions. As for the present skin manifestations, the pigmented patterns with characteristic concave demarcated configurations, their slate-gray or chocolate-brown color, their arrangement in waving lines, networks, whorls, and streaks, and their distribution on the trunk and extremities agree with previous description of this disease (Figs. 1 and 2), while in Case 16 the 22-year-old woman showed instead of the pigmenta-

tion irregularly shaped, zigzag-bordered, splash-like depigmented and slightly depressed spots and streaks, which appeared in early childhood on the chest and upper extremities. Ito [17] named this case incontinentia pigmenti achromians, showing the negative picture of the ordinary incontinentia pigmenti. All the inflammatory changes, such as erythemas, vesicles, and verrucae, are usually localized within the pigmented lesions. In Case 1 the erythemas sometimes extended beyond the boundaries of the pigmentations; nevertheless their outbreak and also the vesicle formation were limited to the pigmentations. In Case 17, the pigmented lesions became swollen and reddened when the baby sweated. In Case 20, the skin also became reddened, and wheals appeared every time the mother who suckled the baby ate beef or mackerel. In Case 8 and in Case 10 the babies showed manifest fading of pigmentation when the former after five years and the latter after one and one-half years were called for reexamination.

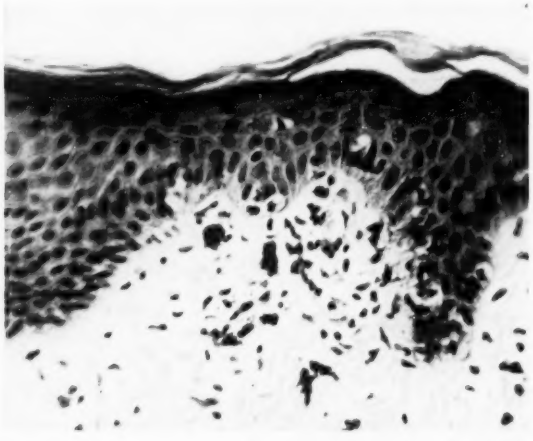

Fig. 3 (Case 9).—Pigmented skin. Vacuole formation and disarrangement of almost depigmented basal cells of the epidermis. Mainly intracellular melanin deposits in the uppermost layer of the corium.

Biopsy revealed in many cases the so-called autochthonous tattooing, that is, the cutaneous mainly intracellular deposition of melanin pigments which were recorded as having dropped down from the epidermis. The streaming down of the epidermal pigments through the epidermodermal junction into the corium was really seen in many cases (Fig. 3). In Case 20, Kawamura found round fairly large dopa-positive cells scattering or crowding in the upper half of the corium. He distinguished them from the intracellular melanin deposition usually seen in many cases and presumed their myeloid origin. In many cases the epidermis, which usually was depigmented or only scantily pigmented, showed disarrangement, karyolysis, and vacuolation of the basal and prickle cells and marked spongiosis leading to intraepidermal vesicle formation (Fig. 4). The specimen taken from the verrucous eruptions disclosed increase of keratinization and acanthosis (Fig. 5). In the corium there were in most cases perivascular and diffuse cellular infiltrates composed of lymphocytes, polymorphonuclear cells, and eosinophiles. There was also frequent cellular invasion of

the epidermis and the intraepidermal vesicles. In Case 1, in which histoeosinophilia was especially manifest, the blood from the reddened pigmentary lesion on the breast showed a 30.0% eosinophilia as contrasted with a 14.0% eosinophilia of the blood from the ear lobe. Also, in Case 15 the blood from the skin lesion showed a 9.0% eosinophilia, while the blood from the ear lobe in this case had a normal value of

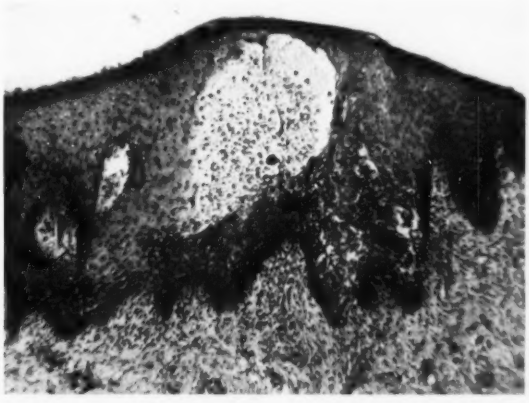

Fig. 4 (Case 1).—Vesicular eruption. Spongiosis and vesicle formation in the acanthotic epidermis. Cellular infiltrates showing marked histoeosinophilia in the upper corium, with clumps of eosinophiles and other types of cells in the intraepidermal vesicle.

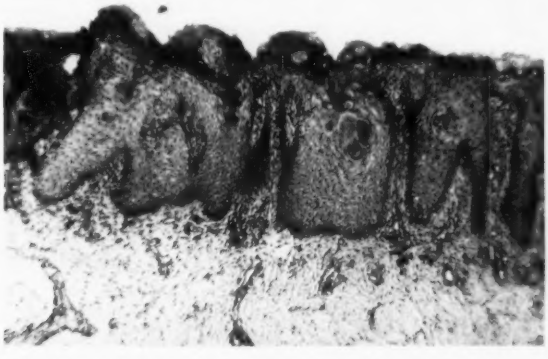

Fig. 5 (Case 1).—Verrucous eruption. Horny layer of the epidermis partially scaled off. Granular layer markedly thickened. Epidermal processes elongated and broadened, showing central cornification. Mainly intracellular melanin deposits and perivascular as well as diffuse infiltrates consisting of lymphocytes, polymorphonuclear cells, and eosinophiles in the upper corium.

eosinophiles. Biopsy of the patient's skin in Ito's Case 16, the so-called incontinentia pigmenti achromians, revealed a complete absence of epidermal and cutaneous melanin deposition in the affected areas.

As regards physiological changes in the affected skin, ultraviolet irradiation and a patch test with potassium-iodide-petrolatum produced in Case 1 only the slightest

inflammation in both the pigmented and the normal skin. The pigmented skin in Case 3 also showed no reaction to ultraviolet irradiation. In Case 16, incontinentia pigmenti achromians, the depigmented-skin areas presented a reduced reaction to histamine in contrast to the accelerated change of the pigmented skin of Case 6 to the same drug. No perspiration was produced after administration of pilocarpine, and the capillary resistance also was reduced in the depigmented skin in Case 16.

While the pigmentation of incontinentia pigmenti usually discolors in the process of time spontaneously with the disappearance of inflammatory changes, the treatment with ascorbic acid (vitamin C) for two months in Case 1 and with trichloroacetic acid and dry ice in Case 7 failed to decrease the pigmentation. In Case 3 the baby was also treated with ascorbic acid injection for four months; during these four months there was no appearance of new lesions and the pigmentation of the extremities was somewhat discolored.

In about half the observed cases, the patients showed simultaneously some congenital and systemic disorders other than the skin manifestations of incontinentia pigmenti. In Case 4, the baby had stupid features and showed slight microcephalus, and she died suddenly of pneumonia. In Case 10, the baby was born in a breech presentation. In Case 11, the baby had frequent colds with convulsions and was also apt to sweat profusely. In Case 8, there was a small congenital hair defect on the vertex; in Case 5 there was a congenital cataract of the left eye. In Case 19 the baby also was found not to have visual acuity. The histologic examination of the removed left eyeball revealed retrolental fibroplasia. The baby soon began to fall very often into convulsions. In Case 20, the baby was affected with metastatic ophthalmia. The left eye soon became blind and showed corneal opacities. In Cases 13, 14, and 15 there was an underdevelopment of teeth. In Case 14, in addition to the outer squint of the right eye accompanying narrow palpebral fissure, there was deformity of the right ear lobe, very thin and sparse hair, and two port-wine marks, one on the right shoulder and the other on the right groin. In Cases 6 and 16, of a 26-year-old woman and a 22-year-old woman, both showed asymmetry of the breasts. There was an eosinophilia of 14.0% in Case 1 and of 7.0% in Case 17.

In considering the pathogenesis of incontinentia pigmenti we should note not merely the skin lesions but also the other congenital and systemic disorders which have been mentioned above. While Yokoyama and Katayama [9] included this disease as a nevus in the broad sense and Minami [14] also interpreted it as a special form of systematized nevus, Kitamura and Chan [6] laid stress on the blood and histoeosinophilia as well as on the vesicle formation in the pigmented skin. Ito [11] postulates from the physiological changes [17] in the affected skin, as shown in his Cases 6 and 16 a congenital dysfunction of the autonomic nervous system and is of the opinion that any inflammatory eruptions of incontinentia pigmenti may occur as the result of the reaction of this congenitally abnormal autonomic nervous system to various stimuli given in the extrauterine environment. He regarded the eosinophilia seen in the case of Kitamura and Chan (Case 1) as a manifestation of abnormal tonus of the autonomic nervous system. The characteristic concave pigmented patterns occur between the terminal nerve endings of the vasomotor nerves, according to Ito. The asymmetry of the breasts seen in Cases 6 and 16 is regarded by Ito as indicating the retarded development of the merocrine glands due to the congenital asymmetry of the trophic nerves.

SUMMARY

Twenty-one Japanese cases, our own 8 plus 13 other cases, of incontinentia pigmenti, their skin manifestations and other congenital and systemic disorders, are summarized for the further consideration of this disease, whose relative frequency among the Japanese people is presumed from the above-mentioned number of the observed cases.

REFERENCES

1. Carney, R. G.: Incontinentia Pigmenti: A Report of 5 Cases and Review of the Literature, A. M. A. Arch. Dermat. & Syph. **64**:126-135, 1951.

2. Epstein, S.; Vedder, J. S., and Pinkus, H.: Bullous Variety of Incontinentia Pigmenti (Bloch-Sulzberger), A. M. A. Arch. Dermat. & Syph. **65**:557-567, 1952.

3. Haber, H.: The Bloch-Sulzberger Syndrome (Incontinentia Pigmenti), Brit. J. Dermat. **64**:129-140, 1952.

4. Findlay, G. H.: On the Pathogenesis of Incontinentia Pigmenti: With Observations on an Associated Eye Disturbance Resembling Retrolental Fibroplasia, Brit. J. Dermat. **64**:141-146, 1952.

5. Kitamura, K.: Jap. J. Dermat. & Venereol. **45**:353, 1939.

6. Kitamura, K., and Chan, S.: Hihu-to-Hirunyo **6**:632-639, 1938.

7. Kitamura, K., and Chan, S.: Über Incontinentia pigmenti: Melanosis corii degenerativa, Dermat. Wchnschr. **108**:598, 1939.

8. Kitamura, K.: Jap. J. Dermat & Venereol. **47**:369, 1940.

9. Yokoyama, K., and Katayama, K.: Rinsho-no-Hihu-Hirunyo **8**:509-514, 674, 1943.

10. Saito, K.: Jap. J. Dermat. & Venereol. **37**:888-889, 1935.

11. Ito, M.: Nihon-Rinsho **4**:644-648, 1946.

12. Ito, M.: Rinsho-Hifuka-Hitsunyokika **5**:163-165, 1951.

13. Ito, M.: Studies on Melanin: X. Incontinentia Pigmenti (Bloch-Sulzberger), Tohoku J. Exper. Med. **54**:67-72, 1951; (Supp.) **55**:52-56, 1952.

14. Minami, S.: Hihu-to-Hitsunyo **12**:206-207, 1950.

15. Kitamura, K., and Fukushiro, R.: Jap. J. Dermat. & Venereol. **61**:119, 1951.

16. Higuchi, K.; Urabe, H.; Hironaka, T., and Hirata, T.: Hihu-to-Hitsunyo **14**:109-112, 1952.

17. Ito, M.: Studies on Melanin: XI. Incontinentia Pigmenti Achromians; A Singular Case of Nevus Depigmentosus Systematicus Bilateralis, Tohoku J. Exper. Med. (Supp.) **55**:57-59, 1952.

18. Bardach, M.: Systematisierte Naevusbildungen bei einem eineiigen Zwillingspaar, Ztschr. Kinder. **39**:542-550, 1925.

19. Nägeli, O.: Familiärer Chromatophorennävus, Schweiz. med. Wchnschr. **57**:48, 1927.

ERYTHEMA MULTIFORME BULLOSUM FOLLOWING PHENYLBUTAZONE TREATMENT FOR ARTHRITIS

Report of a Fatal Case

CAPTAIN ROSS B. CONE
CAPTAIN CHARLES A. HANNIGAN
AND
CAPTAIN RALPH TEICHER
MEDICAL CORPS, UNITED STATES AIR FORCE

SINCE the introduction of phenylbutazone (Butazolidin) to this country from Switzerland in 1951 for the treatment of arthritis and allied disorders, an increasing number of severe reactions due to this drug have been reported. Agranulocytosis, in one case fatal, and a death following a severe sensitivity reaction, with exfoliative dermatitis, have been the most serious toxic reactions reported to date.*

Fishman and Reynolds recently reported a case of exfoliative dermatitis developing in a patient while taking a course of 29 (200 mg.) tablets of phenylbutazone over a one-week period.[6] We believe our case of erythema multiforme bullosum, a severe dermatologic reaction, is probably due to this drug, and therefore should be reported to emphasize the danger of this medication.

REPORT OF CASE

A 44-year-old white housewife was treated at another Air Force Base dispensary for arthritic pains in the fingers, wrists, and low back, which had been present since March, 1953. Salicylates, vitamins, and a two-week course of cortisone produced only transient benefit. X-rays showed slight narrowing of the lumbosacral joint space. The patient was given 50 (100 mg.) tablets of phenylbutazone, to be taken over a two-week period. She was first seen in the Maxwell Air Force Base outpatient department on Oct. 9, 1953, five days after she had completed this course of treament. At this time her arthritic symptoms had improved, but she complained of soreness of the mouth and eyes of one day's duration. Examination revealed conjunctivitis and vesicular lesions in the mouth. She was started on salicylates and diphenhydramine (Benadryl) hydrochloride, but by the following day she had developed a generalized, nonpruritic skin eruption for which she was hospitalized.

Further questioning revealed a history of urticaria following thyroid medication seven years previously, nausea following sulfadiazine, and "dizziness, breathlessness, and depression" following large amounts of acetylsalicylic acid. On one occasion after a penicillin injection, she "turned purple"; subsequent penicillin therapy caused no difficulty. Except for the history of arthritic pains, the patient had enjoyed good health.

On admission, the patient was acutely ill with an oral temperature of 103 F. There were numerous bullae in the mouth, some of which were hemorrhagic or had purpuric bases. The skin of the neck, shoulders, abdomen, and back showed a diffuse morbilliform eruption. Similar lesions were present on the hands and palms, where a tendency to vesiculation was noted. There

From the 3810th United States Air Force Hospital, Maxwell Air Force Base, Montgomery, Ala.

* References 1 to 5.

was a large, edematous, erythematous patch on the lower back. The eyes showed severe bilateral conjunctivitis. The remainder of the physical examination was entirely negative. A diagnosis of erythema multiforme bullosum, probably due to phenylbutazone, was made.

The urine on admissions showed 1+ albumin and a sediment that contained 20 to 30 white blood cells and 2 to 4 red blood cells per high power field. Chest x-ray was normal. Examination of the blood revealed a white cell count of 6,900, with a differential of 84% neutrophiles, 11% lymphocytes, 1% monocytes, 3% eosinophiles, and 1% basophiles; a red cell count of 4,300,000, with 13.5 gm. of hemoglobin and 49% hematocrit, and a platelet count of 209,000. Blood culture was negative.

In addition to acetylsalicylic acid, she was started on crystalline procaine penicillin G (Crysticillin), 300,000 units, given intramuscularly every 12 hours. This was discontinued on the second day to determine whether the persistent temperature elevation might be related to its use. The temperature remained elevated, however, and penicillin was restarted on the 12th hospital day. Because of exquisite soreness of the mouth, the patient was unable to eat after the first hospital day and was maintained on parenteral fluids.

By the second hospital day, there was marked extension of the eruption, with the development of a prominent bullous component, and daily intravenous infusion of corticotropin (ACTH), 20 mg. over 10-hour periods, was started and continued throughout her hospital stay.

Photograph taken on the 13th hospital day in a fatal case of erythema multiforme bullosum.

After the third hospital day, there was coalescence of the skin bullae with desquamation, particularly over pressure areas, leaving raw, oozing, and bleeding surfaces. On the sixth day cortisone therapy, in doses from 200 to 500 mg. daily, was started, and at this time, with improvement in the condition of her mouth, oral oxytetracycline (Terramycin), 1 gm. daily, was added. On the eighth day a venous cut-down, which had been started on the fifth day, was discontinued because of the development of a local thrombophlebitis of the right saphenous vein.

By the 10th hospital day, the patient's face and chest showed new skin formation, but her back was still denuded. Urine output remained good. However, because of difficulty in voiding, an indwelling catheter was placed in the bladder. For a short period blood-tinged urine with mucous shreds was noted.

Further laboratory data follow: blood urea nitrogen, of 16.7 mg. per 100 cc. on the sixth day; serum chlorides (as sodium chloride), of 503 mg. per 100 cc.; carbon-dioxide-combining power of 46 vol.%; total protein of 4.63 gm. per 100 cc., with albumin of 1.62 gm. and globulin of 3.01 gm. per 100 cc. on the 10th hospital day; serum sodium of 123 mEq. per liter, and serum potassium of 5.8 mEq. per liter, on the 13th day. The hemoglobin was never below 13 gm. per 100 cc., and the hematocrit never below 45%. The white cell count varied between 3,700 and 4,600 from the 3d to the 10th hospital day, with normal differential counts. On the 13th hospital day, however, it was 15,200, with 93% neutrophiles, of which 22% were segmented, 61% band

forms, and 10% metamyelocytes. There were 1% eosinophiles, 2% monocytes, and 4% lymphocytes. The neutrophiles showed marked toxic changes. Blood taken for culture the first hospital day was negative.

Despite progressive improvement in her skin condition, the patient continued to run a febrile course. In addition to corticotropin, cortisone, oxytetracycline, and penicillin, the patient received plasma, whole blood, protein hydrolysates, and intravenous fructose and potassium. Locally she was treated with potassium permanganate baths, dilute silver nitrate baths, methylrosaniline chloride (gentian violet), and petrolatum U. S. P. (Vaseline) gauze. She became more and more toxic, and finally died, on the 14th hospital day.

At autopsy, in addition to the skin lesions, there were found in the lungs, kidneys, myocardium, and mitral valve small firm tan-gray lesions, about 3 mm. in diameter, surrounded by zones of intense hyperemia. No purulent matter could be expressed from these lesions, and no culture was taken. Microscopic sections revealed the lesions to be abscesses containing necrotic tissue, cellular detritus, large numbers of mononuclear-type cells, and clusters of bacteria, morphologically resembling staphylococci. The remarkable feature of these lesions was the extreme paucity of polymorphonuclear leucocytes.

It was evident that the abscesses in various organs were of hematogenous origin and unrelated pathogenetically to the mitral lesion, which was recent and unattended by the type of reaction which would give rise to septic emboli.

Sections of the vertebral bone marrow revealed the presence of erythropoietic and leucopoietic elements in increased amounts, with a diminution in marrow fat.

Sections of the skin revealed marked destructive changes, apparently due to the severe infection involving the deeper epithelial layers and upper corium. Intraepithelial vesicle formation was demonstrated. The lesions were overrun with mononuclear cells. Clusters of bacteria were present in the corium. The skin changes were considered to be consistent with a diagnosis of erythema multiforme bullosum with superimposed infection.

The adrenal glands, which grossly appeared to be slightly increased in size, revealed marked decrease in cortical lipid on microscopic examination.

The final pathological diagnoses were as follows: (1) erythema multiforme bullosum, infected; (2) abscesses in lungs, myocardium, and kidneys; (3) early acute bacterial endocarditis of the mitral valve (organism undetermined); (4) hyperplasia of bone marrow.

COMMENT

With the continued use of phenylbutazone in the treatment of various arthritic and muscular disorders, many reports of untoward reactions have appeared in the literature. These have ranged from nausea to fatal agranulocytosis. Skin reactions have been one of the commoner idiosyncrasies encountered with use of this drug. It has been estimated that approximately 3 to 4% of patients receiving phenylbutazone develop a skin eruption, which frequently takes the form of a morbilliform rash. This is said to be of minor import and will supposedly subside rapidly upon discontinuance of the drug and/or desensitization with minute doses.[7] Other dermatologic manifestations include a papular eruption and stomatitis. The severest reaction hitherto reported was that recorded by Nathan and his associates, whose patient developed an exfoliative dermatitis with fatal outcome after 11 days of therapy, including corticotropin.

The present case is the second report of a fatal skin reaction which may be attributable to phenylbutazone. This reaction manifested itself as an erythema multiforme bullosum. The eruption started benignly enough as a stomatitis after the drug had been discontinued for five days, but rapidly evolved as a widespread erythema multiforme bullosum. At its full-blown stage the entire mucous membrane of the mouth showed numerous superficial erosions, many of which were purpuric. The eyes revealed acute catarrhal conjunctivitis, which rapidly became purulent. The

vaginal mucosa was involved in a similar process. The skin lesions, which had started initially as a morbilliform eruption, became bullous, with coalescence and finally denudation of the skin of the back, abdomen, chest, upper extremities, and face. In its terminal phase, with the presence of a Nikolsky sign, the similarity to pemphigus vulgaris was striking, as is often the case in severe erythema multiforme bullosum.

While other antirheumatic drugs, mainly aminopyrine, but also the salicylates, have caused skin eruptions in the past, these have been of relatively rare occurrence, and have largely consisted of benign erythematous lesions. Antipyrine, containing the pyrazole grouping common to phenylbutazone and aminopyrine, has also been reported to cause stomatitis and bullous eruptions.[8] It is now evident that phenylbutazone has severe toxic reactions common to those encountered in the use of aminopyrine and antipyrine, namely, agranulocytosis in the former and bullous skin eruptions in the latter.

SUMMARY

A fatal case of dermatitis medicamentosa of the erythema multiforme bullosum type, the result of a sensitivity reaction to phenylbutazone, is presented.

The striking postmortem findings of probable staphylococcic septicemia with almost no polymorphonuclear response point up the importance of vigorous antibiotic therapy in this type of case. The final cause of death was probably a septic toxemia secondary to a profound bacteremia.

The importance of careful selection of nonallergic patients in the use of this potentially dangerous medication is brought into focus.

The current concept that a drug eruption resulting from phenylbutazone will clear spontaneously with discontinuance of the medication or with administration of antihistaminics and/or adrenal steroids did not prove true in this case.

CONCLUSION

The increasing number and severity of reactions to phenylbutazone, and the absence of conclusive evidence of its specificity in rheumatic disorders, warrant a careful reconsideration of the use of this drug.

REFERENCES

1. Stifel, J. L., and Burnheimer, J. C.: Agranulocytosis Following Administration of Phenylbutazone (Butazolidin®), J. A. M. A. **151**:555 (Feb. 14) 1953.

2. Bershof, E., and Oxman, A. C.: Agranulocytosis Following Use of Phenylbutazone (Butazolidin®), J. A. M. A. **151**:557 (Feb. 14) 1953.

3. Werblow, S. C., and Neber, J.: Agranulocytosis Following Phenylbutazone Therapy, J. A. M. A. **151**:1286 (April 11) 1953.

4. Etess, A. D., and Jacobson, A. S.: Fatality Due to Agranulocytosis Following Use of Phenylbutazone (Butazolidin®), J. A. M. A. **151**:639 (Feb. 21) 1953.

5. Nathan, D. A.; Meitus, M. L.; Capland, L., and Lev, M.: Death Following Phenylbutazone (Butazolidin) Therapy, Ann. Int. Med. **39**:1096 (Nov.) 1953.

6. Fishman, H. C., and Reynolds, J.: Exfoliative Dermatitis Following Ingestion of Phenylbutazone (Butazolidin), J. A. M. A. **153**:642 (Oct. 17) 1953.

7. Kuzell, W. C., and Schaffarzick, P. W.: Phenylbutazone (Butazolidin®), Bull. Rheumat. Dis. **3**:23 (Nov.) 1952.

8. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, p. 219.

ISONIAZID (ISONICOTINIC ACID HYDRAZIDE) IN SKIN TUBERCULOSIS

Preliminary Report of Sixteen Cases

FERNANDO LATAPI, M.D.
ERNESTO ESCALONA, M.D.
OBDULIA RODRÍGUEZ, M.D.
MEXICO, D. F., MEXICO
AND
SANTIAGO CASTRO ESTRADA, M.D.
NEW BRUNSWICK, N. J.

AS WE BECAME aware of the remarkable activity demonstrated by isoniazid (isonicotinic acid hydrazide) against Mycobacterium tuberculosis in vitro * as well as in vivo, both in experimental infections † and in human beings,‡ we decided to study the therapeutic activity of this drug in different clinical varieties of skin tuberculosis. This preliminary note refers to the observations made from April, 1952, to the end of January, 1953, at the Department of Dermatology of the General Hospital and at the Centro Dermatológico Pascua in Mexico City.

MATERIAL

In a nine-month period 16 patients were treated, 9 males and 7 females. Their ages varied between 8 and 84 years. Four were suffering from lupus vulgaris, four from tuberculosis verrucosa cutis, four from tuberculosis colliquativa, two from papulonecrotic tuberculid, one from tuberculosis indurativa, and one from tuberculosis fungosa.

The duration of the disease varied from 18 months (tuberculosis colliquativa of the neck) to 40 years (lupus vulgaris of the arm). All the patients presented definite cutaneous lesions in different degrees of activity, but all were active enough to make possible the observation of changes during treatment. In general, they did not show evidence of active visceral tuberculosis except one case suffering from tuberculosis colliquativa in whom a clinical and radiological examination showed lesions of pulmonary tuberculosis.

METHODS

Study of Cases.—A clinical history was recorded in every instance. The pertinent laboratory examinations performed were as follows: bacterioscopic studies, and cultures in Löwenstein's medium of material taken from the lesions, Mantoux tests, histopathological studies of biopsies, blood counts, and urine analysis.

Therapy Employed.—Isoniazid was administered in 100 mg. tablets of Nydrazid. Dosage varied from 3 to 8 mg. per kilogram of body weight per day. No other drug known to have antitubercular activity was used concomitantly.

Of these 16 cases, 8 were submitted to treatment for more than six months, 7 for two to four and a half months, and 1 for one month only.

Isoniazid (Nydrazid) was supplied by E. R. Squibb & Sons de México, S. A. de C. V.

From the Hospital General and Centro Dermatológico Pascua. (Dr. Latapi, Dr. Escalona, and Dr. Rodríguez) and the Squibb Institute for Medical Research (Dr. Estrada).

* References 1 and 2.

† References 3, 4, and 6.

‡ References 6 to 9.

TABLE 1.—*Material*

Case	Sex	Age, Yr.	Diagnosis	Time with the Disease, Yr.
1	M	35	Tuberculosis verrucosa cutis	30
2	M	31	Tuberculosis verrucosa cutis	25
3	F	58	Tuberculosis verrucosa cutis	10
4	M	15	Tuberculosis verrucosa cutis	5
5	M	22	Lupus vulgaris	10
6	F	8	Lupus vulgaris	2
7	M	21	Lupus vulgaris	13
8	F	84	Lupus vulgaris	40
9	F	35	Tuberculosis fungosa	2
10	M	17	Tuberculosis colliquativa	1 1/2
11	M	22	Tuberculosis colliquativa	1 1/2
12	M	17	Tuberculosis colliquativa	2
13	M	15	Tuberculosis colliquativa	1 1/2
14	F	20	Papulonecrotic tuberculid	6
15	F	27	Papulonecrotic tuberculid	18
16	F	32	Tuberculosis nodulo indurativa	16

TABLE 2.—*Results of Treatment*

Case	Diagnosis	Dose per Kg. of Body Weight per Day, Mg.	Duration of Treatment, Mo.	Degree of Improvement
1	Tuberculosis verrucosa cutis	4	2	++*
2	Tuberculosis verrucosa cutis	5	7	Clinically cured
3	Tuberculosis verrucosa cutis	5	4 1/2	Clinically cured
4	Tuberculosis verrucosa cutis	8	3	Clinically cured
5	Lupus vulgaris	3	7	++
6	Lupus vulgaris	3	7	Clinically cured
7	Lupus vulgaris	5	2	+†
8	Lupus vulgaris	5	3	++
9	Tuberculosis fungosa	4	1	+
10	Tuberculosis colliquativa	4	7 1/2	++
11	Tuberculosis colliquativa	5	6	++
12	Tuberculosis colliquativa	4	4 1/2	Clinically cured
13	Tuberculosis colliquativa	5	2 1/2	+
14	Papulonecrotic tuberculid	4	7	++
15	Papulonecrotic tuberculid	4	6 1/2	++
16	Tuberculosis indurativa	5	7	+

* ++ indicate remarkable improvement.
† + indicates improvement.

Fig. 1 (Case 4).—Tuberculosis verrucosa cutis. *A*, before treatment; *B*, one month after initiation of treatment; *C*, biopsy of lesion prior to treatment; *D*, biopsy of lesion after three months of treatment.

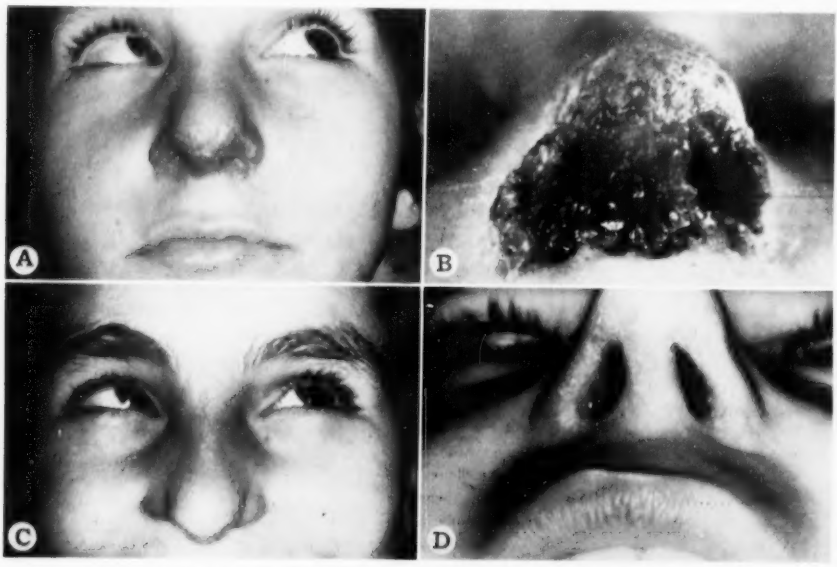

Fig. 2 (Case 6).—Lupus vulgaris. *A*, before treatment; *B*, before (close-up); *C*, after three months of treatment; *D*, after three months of treatment (close-up).

RESULTS

In general, remarkable results were obtained. In five of our patients the lesions cleared up completely, leaving only cicatricial sequelae, keloidal in two cases. In others, there was evident reduction in the activity of the lesions. The favorable results occurred more rapidly in cases with tuberculosis verrucosa cutis and lupus vulgaris (Figs. 1, *A* and *B*, 2, and 3, *A* and *B*).

All the cases of tuberculosis colliquativa were improved, and one patient was clinically cured. However, these results were apparently obtained less rapidly than in the two latter clinical varieties of the disease. The hematogenous forms, in which the results of any treatment are difficult to evaluate, showed, nevertheless, evident favorable changes.

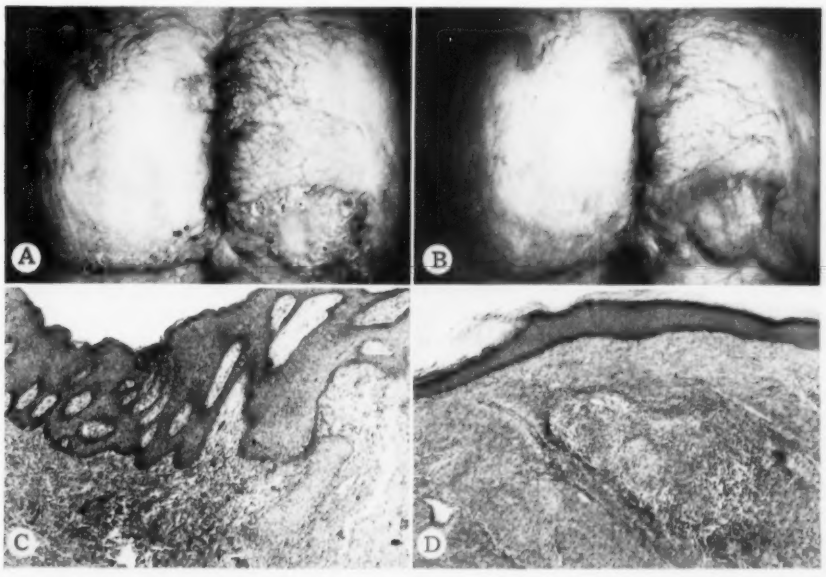

Fig. 3 (Case 2).—Tuberculosis verrucosa cutis. *A*, before treatment; *B*, three months after initiation of treatment; *C*, biopsy of lesion prior to treatment; *D*, biopsy of lesion after three months of treatment.

We are including in this report a case of tuberculosis fungosa which has received treatment for one month only, in view of the fact that despite the short duration of treatment definite favorable modifications were evident.

The histopathological changes which have occurred so far have paralleled the clinical results. In general, a frank diminution of the specific infiltrate has been observed, but not its complete disappearance (Figs. 1,*C* and *D*, 3 *C* and *D*).§

Increases in weight, which varied from 1 to 14 kg. in these few months, have been observed in our patients.

The drug was well tolerated in all instances.

§ The study of these changes was made by Dr. M. Martínez Báez and Dr. A. Chévez.

It is possible that the therapeutic value of isoniazid might be reinforced by combination with other antitubercular drugs. In this study we did not try to find out if resistant strains might develop during treatment.

SUMMARY AND CONCLUSIONS

Results on isoniazid (Nydrazid) treatment of 16 cases ‖ of skin tuberculosis are given. From the observations made, we wish to emphasize the following facts:

1. Isoniazid has shown a frank therapeutic activity in doses of from 3 to 8 mg. per kilogram of body weight per day in all the cases of skin tuberculosis reported.

2. This therapeutic activity has been equal and in some cases undoubtedly superior to that of other treatments previously employed in skin tuberculosis.

3. No evidence of intolerance to the drug was observed.

The results obtained justify the continuation and widening of this study to properly evaluate the beneficial effects so far observed from the use of isoniazid in skin tuberculosis.

‖ Dr. Jorge Carvallo did the study and control of Case 6.

REFERENCES

1. Pansy, F.; Stander H., and Donovick, R.: In Vitro Studies on Isonicotinic Acid Hydrazide, Am. Rev. Tuberc. **65**:761, 1952.

2. Steeken W., Jr., and Wolinsky, E.: Antituberculous Properties of Hydrazines of Isonicotinic Acid (Rimifon, Marsilid), Am. Rev. Tuberc. **65**:365, 1952.

3. Bernstein, J.; Lott, W. A.; Steinberg, B. A., and Yale, H. L.: Chemotherapy of Experimental Tuberculosis: V. Isonicotinic Acid Hydrazide (Nydrazid) and Related Compounds, Am. Rev. Tuberc. **65**:357, 1952.

4. Grunberg, E., and Schnitzer, R. J.: Studies on the Activity of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice, Quart. Bull. Sea View Hosp. **13**:3, 1952.

5. Grunberg E.; Leiwant, B.; D'Ascensio, I. L., and Schnitzer, R. J.: On the Lasting Protective Effect of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculous Infection of Mice, Dis. Chest **21**:369, 1952.

6. Elmendorf, D. F.; Cawthon, W. U.; Muschenheim, C., and McDermott, W.: The Absorption, Distribution, Excretion, and Short-Term Toxicity of Isonicotinic Acid Hydrazide (Nydrazid) in Man, Am. Rev. Tuberc. **65**:429, 1952.

7. Robitzek, E. H.; Selikoff, I. J., and Ornstein, G. G.: Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid (Preliminary Report of Representative Cases), Quart. Bull. Sea View Hosp. **13**:27, 1952.

8. Selikoff, I. J., and Robitzek, E. H.: Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid, Dis. Chest **21**:385, 1952.

9. Robitzek, E. H., and Selikoff, I. J.: Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid) in the Treatment of Active Progressive Caseous-Pneumonic Tuberculosis: A Preliminary Report, Am. Rev. Tuberc. **65**:402, 1952.

ACNE COMEDO IN CHILDREN DUE TO PARAFFIN OIL APPLIED ON THE HEAD

CHAIM BERLIN, M.D.
TEL AVIV, ISRAEL

FROM AMONG the various factors which help to produce acne vulgaris, the most important are, undoubtedly, the sex hormones, and it therefore occurs principally during puberty. The androgens are especially acnegenic because of their stimulating effect on the pilosebaceous apparatus, as is clearly shown clinically and experimentally in rats [1] and in human beings.* The usual premenstrual flare-up of the disease is explained by some investigators by the fact that in this period the amount of folliculin in the blood is at its lowest level with the result that the normal androgen-estrogen balance is altered in favor of androgen.

It is very likely that acne neonatorum, too, can be partially explained on a hormonal basis. The blood of a pregnant woman contains great quantities of estrogens, which readily pass through the placenta, enter the fetal bloodstream, and then in the newborn sometimes cause infantile seborrhea and, occasionally, also acne. Here, on the contrary, the estrogens are to blame. Seemingly, these cases are rare instances of what Sulzberger and Baer [4] called "estrogen acne." These authors observed the appearance of acne in persons who, for some reason, received estrogen therapy. Perlman [5] described two infants, aged 1 week and 3 months, respectively, with typical acne vulgaris associated with mastitis neonatorum.

However, in children older than 1 year, in whom the maternal and their own sex hormones are naturally not active, the sometimes observable acne must be provoked by other factors. English writers † described acne in children, caused by using camphorated oil.

Recently I had the opportunity to observe a number of children with an acneform eruption on the face. In searching for the cause, I soon discovered that the offending agent was paraffin oil, which was applied to the head after washing, and which on chemical examination proved to be impure.

Two of the cases observed first, are presented here.

REPORT OF CASES

CASE 1.—K. D., a boy, aged 5 years, from a *kvutza* (collective agricultural settlement) was seen in the Dermatological Clinic of the hospital with an acnelike eruption of the face of two months' duration. It started with tiny papules which gradually increased in number, covering the forehead, the chin, the cheeks, and the ears, especially the lobes. The eruption

From the Department of Dermatology, Municipal Hospital, Hadassah.

* References 2 and 3.

† References 6 to 9.

was rather uniform and consisted of pinhead-sized papules, confined to the follicles. Some showed black points in the center, others a perifollicular inflammation. On the body there were several plaques of keratosis pilaris. The eye examination showed nothing abnormal. Nevertheless, a vitamin A deficiency was considered. Vitamin A, 200,000 units daily, was given internally, and an ointment containing salicylic acid and precipitated sulfur was used. There was no essential change after three weeks. The blackheads increased in number, and with a comedo extractor short comedos could be expressed. There were also several typical acne pustules. The child was presented at the meeting of the Dermatological Society as a case of acne in a child of unknown cause.

Case 2.—S. B., a boy, aged 2 years, from the same *kvutza* was referred to the clinic on May 14, 1953, because of an eruption of the face of several months' duration. The cheeks, forehead, chin, and ears presented a number of comedos, miliary cysts, pitted scars, and several distinct acne pustules. On the right cheek, there was a bluish-red cyst like lesion of the size of a hazelnut, which secreted a purulent bloody fluid (Fig. 1).

The nurse of the *kvutza* stated that more children of the settlement were similarly affected. I visited the settlement and examined all the children with the assistance of the attendant physician and the nurses.

Fig. 1. (Case 2).—Pitted scars, milia, and comedos in a 2-year-old boy. Note the bluish purulent cyst near the right eye.

Twenty-six children, 16 boys and 10 girls of the ages of 2 to 10 years (average, 6 years) were found to be affected, approximately 25% of all the children of the same age in the settlement.

The first signs of this epidemic-like disease appeared about half a year before in the form of several papules in several children. The condition gradually deteriorated and more children became involved.

The morphologic picture was rather uniform, with some variations in degree. In general, the males were more severely affected. The eruption was limited to the face. The cheeks were involved in all cases; next in intensity came the forehead, the helices and lobes of the ears (never the insides of the ears), the chin, and the nose. The individual lesions were milia, but chiefly pinhead-sized, skin-colored, conical papules. Most of them had black points, and with an "expressor," a short comedo-like mass could be expressed. A few lesions showed signs of inflammation; here and there real acne papules and pustules were present. The lesions were fre-

quently arranged in groups, especially on the cheeks, and on palpation they felt like a grater (Fig. 2). The eruption was asymptomatic and apparently not handled by the patients.

The disease was distinguished from the adolescent type of acne by (1) the fairly uniform character of the eruption; (2) the definite predominance of comedos; (3) the frequent grouping of the lesions, especially on the cheeks; (4) the lack of seborrhea and (5) the lack of involvement of the back and chest. The disease resembled rather keratosis follicularis "epidemica" of the Swiss authors,‡ which broke out like an epidemic in 1946 in Basel and mostly affected the face in children. Its cause remained mysterious. Schenker [12], however, found symptoms of this disorder in patients in mental asylums. They were occupied in separating tin foil from tissue paper, attached by an adhesive material composed of a new mixture of wax and paraffin. It was observed that patients stroked their faces with the foil.

It is obvious that a common causal factor had provoked the disease in the children. An internal, dietetic or deficiency factor could easily be excluded. The chil-

Fig. 2.—Grouped comedos on the face in a 5-year-old boy.

dren were well nourished and they enjoyed good health. No specially treated food was used, and there was no apparent unusual incidence of acne among the youth of the settlement. No oils or ointments were applied on the face. But on inquiry, the nurse in charge stated that for more than half a year the heads of the children had been treated with paraffin oil after the weekly washing of the hair, in order to soften it; previously olive oil had been used. As a matter of fact, the disease broke out shortly after paraffin oil was applied. In support of this assumption was the fact that two children who presented the rash only on one side of the face were in the habit of sleeping only on that side.

The paraffin oil looked apparently clean and clear. It was sent for examination to the pharmaceutical and chemo-analytical labortory for testing of medical materials. The reaction for readily carbonized substances was positive, which meant that a definite unspecified impurity was present.

The use of the oil was immediately stopped. The children were ordered to wash the face frequently and salicylic acid and resorcinol spirits were applied. No essential

‡ References 10 and 11.

change occurred after three weeks, although a certain diminishing of comedos took place. An almost complete cure was achieved when a comedo extractor was used and also benzine to dissolve the oil.

It is well known that oil is acnegenic, but it should be realized that oil applied on the hair can have the same effect. While one is lying down, the pillow is saturated with oil, which naturally comes in contact with the face. Dexter [13] warns against oily hair dressings because of the danger of acne. Sulzberger and Baer [14] call oily substances on the hair, "hidden" factors which provoke and aggravate acne. Garnier [15] described comedos on the face of children and adults, after using brilliantine on the hair, and Gougerot and his associates [16] and Tzank and his co-workers [17] spoke of epidemic occurrence of acne after use of Brilliantine.

Basically, the mechanism of acne is the closing of the pores with oil. In the ordinary acne this is caused by the grease of the sebaceous glands. In the cases reported here this was done by oil from an external source. In the ordinary acne the production of sebum continues, and finding no outlet, causes stagnation, accompanied often by inflammation through Staphylococcus infection. In the cases reported no sebum production occurs; the comedos remain unchanged like foreign bodies, causing inflammatory reaction but rarely. There exists here a certain analogy with the comedos of elderly people, which persist unchanged because of the lack of sebum production.

Another point: Is one entitled to call this disease acne? Recently, Giknis, Hall, and Tolman [18] reviewed and gave two separate tables of acne neonatorum (17 cases) and "grouped comedos" in children (12 cases) collected from the literature. The authors excluded from the second group five cases, two because of the older age of the children, and three because the acne was provoked by camphorated oil; the remaining seven they added to acne neonatorum, which they consider a real acne of probably hormonal nature. Admittedly a hormonal factor may play some role in acne neonatorum, but, on the other hand, there is clinical evidence, such as predominance of comedos and the sole involvement of the face, that here, too, oil applied not necessarily on the face but on the head, may take a share in the causation of the disease. There is a bad habit of mothers and nurses of putting oil on the heads of infants.

In the lists of Giknis and his associates, there was a distinct preponderance of males. Out of 26 of our children, 16 were boys, who were also more severely affected. This would seem to indicate that from the beginning the pilosebaceous apparatus in males is more developed.

SUMMARY

An epidemic outbreak of an acneform eruption is described, which occurred in 26 children of a collective agricultural settlement, 16 boys and 10 girls aged 2 to 10 years. The eruption was located only on the face and was characterized by milia, comedos which often showed grouping, and occasional acne papules and pustules. The disease was caused by weekly application to the hair of paraffin oil, which on chemical examination proved to contain impurity.

The belief is expressed that oil applied to the head (not necessarily to the face) may be a causal factor also in acne neonatorum. The preponderance of males in infantile acne implies that from the beginning the pilosebaceous system in males is more developed.

REFERENCES

1. Hooker, C. W., and Pfeiffer, C. A.: Effect of Sex Hormones upon Body Growth, Skin, Hair and Sebaceous Glands in the Rat, Endocrinology **32**:69 (Jan.) 1943.

2. Rony, H. R., and Zakon, S. J.: Effect of Androgen on the Sebaceous Glands of the Human Skin, Arch. Dermat. & Syph. **48**:601 (Dec.) 1943.

3. Rony, H. R., and Zakon, S. J.: Effect of Endocrine Substances on the Adult Human Scalp, Arch. Dermat. & Syph. **52**:323 (Oct.) 1945.

4. Sulzberger, M. B., and Baer, R. L.: Acne Vulgaris and Its Management, the 1949 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1949, p. 9.

5. Perlman, H. H.: Acne Neonatorum: Report of Acne Vulgaris in 2 Infants, J. Pediat. **33**:609 (Nov.) 1948.

6. MacLeod, J. M. H.: Case Presentation, Brit. J. Dermat. **17**:141 (April) 1905.

7. MacLeod, J. M. H.: Grouped Comedones in an Infant, Brit. J. Dermat. **30**:181 (July-Sept.) 1918.

8. Dore, S. E.: Multiple Comedones in a Child Aged Thirteen Months, Brit. J. Dermat. **21**:220 (July) 1909.

9. Gray, A. M. H.: Acne in a Child Aged 2 Years, Proc. Roy. Soc. Med. **27**:292 (Nov. 16) 1933.

10. Schuppli, R.: Über eine mit starker Komedonbildung verlaufende Epidemie von Keratosis follicularis bei der Bevölkerung von Basel und Umgebung, Schweiz. med. Wchnschr. **76**:678 (July 27) 1946.

11. Lutz, W.: Keratosis follicularis "epidemica," in Lehrbuch der Haut-und Geschlechtskrankheiten, Basel, S. Karger, 1951, p. 11.

12. Schenker, O.: Beobachtungen zur Basler Krankheit, Dermatologica **97**:35, 1948.

13. Dexter, H.: Studies in Acne: The General Practitioner's Role in Topical Therapy of Acne Vulgaris, J. A. M. A. **142**:715 (March 11) 1950.

14. Garnier, G.: Boutons d'huile du visage par brillantine, Bull. Soc. franç. dermat. et syph., p. 84, March 3, 1944.

15. Garnier, G.: Les comedons, d'huile et boutons d'huile du visage par brillantine, Presse. méd. **54**:146 (March 9) 1946.

16. Gougerot, H.; Carteaud, A., and Grupper: "Epidémie" de comédons par les brillantines, crèmes etc. de gérer, Bull. Soc. franç. dermat. et syph., p. 286, Nov. 8, 1945.

17. Tzank, H.; Sidi, E., and Dobkevitch, S.: Nombreux cas d'éruption acneiform provoqués par une brillantine de fabrication récente, Bull. Soc. franç. dermat. et syph., p. 293, Nov.-Dec., 1945.

18. Giknis, F. L.; Hall, W. K., and Tollmann, M. M.: Acne Neonatorum, A. M. A. Arch. Dermat. & Syph. **66**:717 (Dec.) 1952.

ANALGESIC EFFECTS OF CORTISONE AND HYDROCORTISONE

F. B. BENJAMIN, D.M.D., Ph.D.
AND
THEODORE CORNBLEET, M.D.
CHICAGO

IN A PREVIOUS investigation [1] on the local effect of intracutaneously injected cortisone we found that cortisone exhibited some local anesthetic action. Meanwhile, several papers have appeared on the local anti-inflammatory action of hydrocortisone.* Goldman, Emura, and Baskett [3] believe it possible that the anti-inflammatory effects of cortisone may be due to hydrocortisone as a peripheral cortisone metabolite. This suggests an investigation of the analgesic properties of hydrocortisone as compared to cortisone. It was hoped that such an investigation would throw light on the mechanism of the therapeutic effect of cortisone and also that it would give us some clues as to the mechanism of peripheral pain. For this purpose it was thought worth while to compare these compounds in combination with procaine and antihistaminic agents.

PROCEDURE

In the studies reported here pain was produced by the intradermal injection of (1) thiamine hydrochloride, 100 mg. per cubic centimeter (Abbott); (2) crude liver extract (Armour); (3) histamine phosphate, 1 mg. per cubic centimeter (Abbott).

The following substances were tested as to their relative ability to produce pain inhibition: (1) cortisone acetate, 25 mg. per cubic centimeter (Merck), and cortisone acetate, 25 mg. per cubic centimeter (Upjohn); (2) hydrocortisone acetate, 25 mg. per cubic centimeter (Merck), and hydrocortisone acetate, 25 mg. per cubic centimeter (Fadrenal, G. D. Searle); (3) suspension medium for cortisone (Merck), which contains 0.9% benzyl alcohol, and suspension medium for cortisone (Upjohn), which contains 1.5% benzyl alcohol; (4) diphenhydramine (Benadryl) hydrochloride, 10 mg. per cubic centimeter (Parke, Davis); (5) chlorprophenpyridamine (Chlor-Trimeton), 100 mg. per cubic centimeter (Schering); (6) procaine hydrochloride, 1%.

The subjects for these experiments were medical and graduate students. Most of these students had been used for previous pain experiments and were trained for interpretation of fine differences in pain perception. They were not familiar with the nature of the experiments or with the substances being tested. The sequence of injections was changed in a random fashion.

In general the subjects compared the pain-producing effects of the pain-producing substance when it was injected alone (control) with the pain-producing effects when it was injected along with the experimental substance. The pain produced was assessed by the patient according to the following categories:

−1	more pain than the control
0	same degree of pain as control
+1	slight inhibition of pain
+2	marked inhibition of pain
+3	no pain

The site tested was the volar surface of the forearm.

From the Departments of Clinical Science and Dermatology, University of Illinois College of Medicine and the Cook County Hospital.

* References 2, 3, 5, and 7.

Early in the investigation it was found that there was a time difference in the relative analgesic action of the various substances under investigation. Therefore two procedures were used.

1. The analgesic agent (0.05 cc.) was injected with the pain-producing substance (0.1 cc.) as one intradermal injection. This effect is subsequently called the "immediate analgesic effect."

2. The analgesic agent (0.25 cc.) was injected subcutaneously three minutes before the pain-producing substance (0.1 cc.) was injected intradermally in the same area. This procedure is subsequently called "later analgesic effect."

In addition to the observations on pain the effect of these substances on the inhibition of the histamine-induced skin flare was determined. In this test 0.05 cc. of the experimental substance was added to 0.1 cc. of histamine phosphate, the mixture being injected intradermally.

RESULTS

Chart 1 shows the results of 90 experiments on the "immediate analgesic effect." An inspection of the chart indicates some analgesic effects of cortisone and hydro-

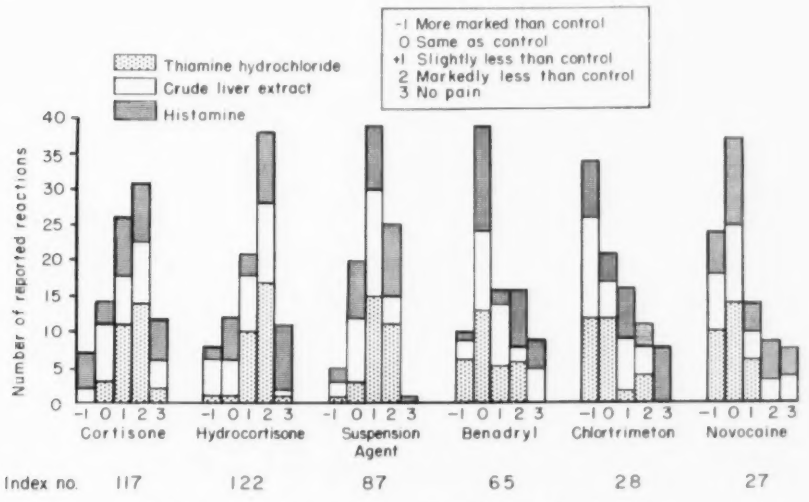

Chart 1.—Immediate analgesic effect (instant of injection).

cortisone and a slight effect by the suspension medium and diphenhydramine. It was considered necessary to show these effects in a more mathematical form. Therefore an index number was obtained by multiplying the total number of reported pain reactions in each column by the column categories and adding the products for any substance. For instance, in Chart 1 the first column for cortisone is marked —1 (pain more marked than control). The total number of observations is seven. Then $7 \times (-1)$ is -7. In the next column, $14 \times 0 = 0$; in the third column, $1 \times 26 = 26$; in the fourth column, $2 \times 31 = 62$, and in the fifth column $3 \times 12 = 36$. The sum $(-7, 0, 26, 62, 36)$ is 117, the "index number," and gives a comparative value of pain inhibition.

As this "index number" gives comparative values only restricted to experiments with the same number of observations, another figure mean, "pain index," is given

in Table 1. This is obtained by dividing the index number by the total number of observations. In Table 1, first column, the index number is 117. The total number of observations is 90. Then, the mean pain index is $117/90 = 1.3$.

For skin flare a similar index number was obtained by multiplying the number of observations in each column with the column value and adding the products in each group. The index number divided by the number of observations gives the mean inhibition index.

We can conclude from these results (Chart 1 and Table 1) that under the given conditions cortisone and hydrocortisone have a marked analgesic effect. The suspension medium and diphenhydramine have some effect, while procaine hydrochloride (Novocain) and chlorprophenpyridamine have no effect.

The suspension medium prepared by Upjohn was slightly more effective than the Merck preparation, and the hydrocortisone from G. D. Searle had more analgesic effect than that obtained from Merck. These differences were not significant.

TABLE 1.—*Tests of Analgesic Effects*

Pain-Producing Agent	Analgesic Agent Tested: Cortisone	Hydrocortisone	Suspension Medium	Diphenhydramine	Chlorprophenpyridamine	Procaine Hydrochloride
A. Immediate Analgesic Effect (Mean Index)*						
Thiamine	1.4	1.53	1.2	0.37	−0.07	−0.13
Liver extract	1.5	0.93	0.7	0.83	0.03	0.47
Histamine	1.23	1.60	1.0	0.97	0.97	0.57
Total	1.30	1.36	0.97	0.72	0.31	0.30
S. E.	0.124	0.136	0.085	0.163	0.202	0.164
B. Later Analgesic Effect (Mean Index)*						
Thiamine	2.2	2.0	1.4	2.0	2.6	3.0
Liver extract	2.2	2.4	1.6	1.4	2.4	3.0
Histamine	1.4	2.0	1.8	1.4	2.6	2.8
Total	1.94	2.20	1.60	1.60	2.60	2.93
S. E.	0.203	0.183	0.185	0.238	0.225	0.022
C. Inhibition of Skin Flare (Mean Inhibition Index)†						
Total	1.0	1.13	0.27	1.0	2.0	0.2
S. E.	0.145	0.190	0.190	0.095	....	0.143

* For definition of pain index, see text. The greater this number the greater is the analgesic effect observed.
† For definition, see text. The greater the number the greater is the inhibition of skin flare.

Thiamine hydrochloride appears to be the most suitable substance to bring out differences of pain sensation. In the thiamine group the addition of chlorprophenpyridamine and of procaine hydrochloride enhanced the immediate pain.

Chart 2 shows the results obtained with the "later analgesic effect." Table 1B shows the corresponding mean pain index. Under these conditions the hormones have some analgesic effect, but at this time it is not as pronounced as the effect of chlorprophenpyridamine and procaine hydrochloride. Diphenhydramine and the suspension medium have some effect but clearly less than that of the other substances.

Chart 3 shows the inhibition of skin flare. Table 1 C gives the index numbers for these reactions. The pattern of reactivity is different from that of the pain reaction. Chlorprophenpyridamine produces the most intense inhibition of skin flare. Hydrocortisone, cortisone, and diphenhydramine have some inhibitory ability, while the suspension medium and procaine hydrochloride have no effect. It may be pointed out that the histamine itch was not significantly decreased by any agent nor was

the histamine inhibited. This is in contradiction to the findings of Loew [6] and others, who found that the histamine itch and wheal are inhibited by antihistaminics. This result may be due to a difference of procedure.

Table 2 indicates which of the observed differences are statistically significant at the 5.0% level. The difference between cortisone and hydrocortisone is not significant for any of the reactions studied. The immediate analgesic effect of the

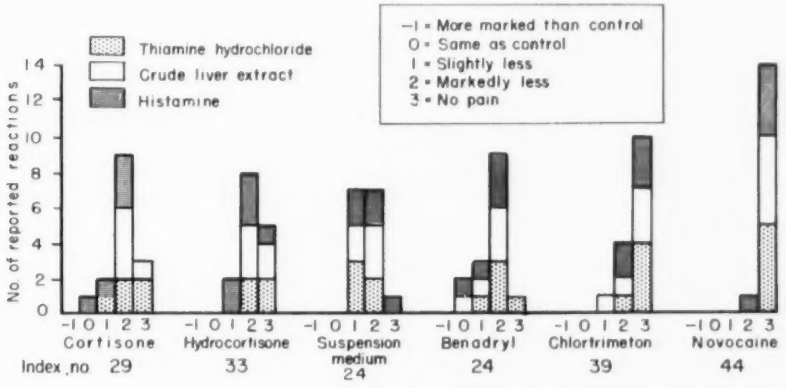

Chart 2.—Later analgesic effect (3 minutes after injection).

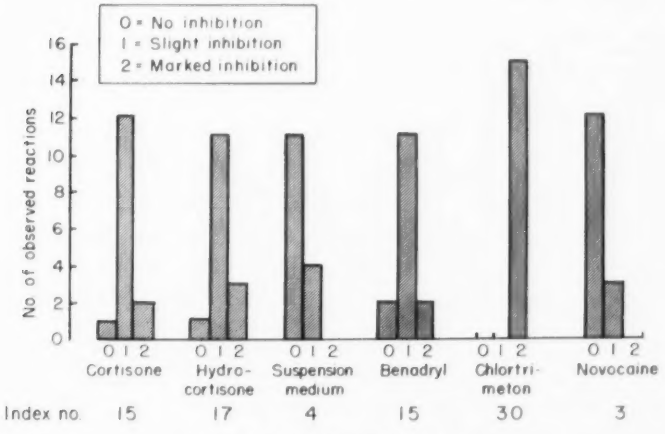

Chart 3.—Inhibition of skin flare.

hormones is significantly greater than that of any other of the substances tested here. The later analgesic effects of the hormones are marked but not as pronounced as those of chlorprophenpyridamine and procaine hydrochloride.

These findings indicate that the mechanism of the analgesic action of the adrenocortical hormones studied is different from that of the antihistaminics and of the local anesthetics. In pain production, according to Sir Thomas Lewis, the painful stimulant does not act on the pain receptors directly but via some chemical mediator,

probably some histamine-like substance. If this is true, it would indicate three possible mechanisms for the analgesic effect of cortisone. 1. Cortisone may decrease the amount of pain substance released; 2. cortisone may interfere with the activity of this pain substance, or 3. cortisone may decrease the sensitivity of the nerve endings to this pain substance.

The fact that the hormones exert their analgesic action quickly, at a time when procaine hydrochloride has had as yet no time to act, indicates that the hormones act at an early stage in the above scheme. The inhibition of immediate pain appears to

TABLE 2.—*Significance of Difference*

	Immediate Analgesia	Later Analgesia	Inhibition of Skin Flare
Cortisone—hydrocortisone	.....	.....	.....
Cortisone—suspension medium	+(Co)*	.....	+(Co)
Cortisone—diphenhydramine	+(Co)	.....	.....
Cortisone—chlorprophenpyridamine	+(Co)	+(Ch)	+(Ch)
Cortisone—procaine hydrochloride	+(Co)	+(N)	+(Co)
Hydrocortisone—diphenhydramine	+(H)	+(H)	.....
Hydrocortisone—suspension medium	+(H)	+(H)	+(H)
Hydrocortisone—chlorprophenpyridamine	+(H)	.....	+(Ch)
Hydrocortisone—procaine hydrochloride	+(H)	+(N)	+(H)
Suspension medium—diphenhydramine	.....	.....	+(B)
Suspension medium—chlorprophenpyridamine	+(SM)	+(Ch)	+(Ch)
Suspension medium—procaine hydrochloride	+(SM)	+(N)	.....
Diphenhydramine—chlorprophenpyridamine	.....	+(Ch)	+(Ch)
Diphenhydramine—procaine hydrochloride	.....	+(N)	+(B)
Chlorprophenpyridamine—procaine hydrochloride	.....	.....	+(Ch)

* The abbreviation shows which of the two substances is more effective.

be different in nature from the inhibition of later pain and the inhibition of skin flare. This becomes clear if we condense the results as follows:

	Inhibition of Immediate Pain	Inhibition of Later Pain	Inhibition of Skin Flare
Cortisone	++	+	+
Chlorprophenpyridamine	0	++	+++
Procaine hydrochloride	0	+++	0

An indication of the nature of this difference may be found in Menkin's work,[7] where it was demonstrated that compound F counteracts leucotaxine and the leucocytosis-promoting factor but does not affect exudine. Further studies are needed to elucidate the mechanisms of the reactions studied.

SUMMARY

The local effects of cortisone and hydrocortisone were compared with those of their suspension medium, of antihistaminics, and of procaine hydrochloride (Novocain) as to their (1) immediate analgesic properties, (2) later analgesic properties, and (3) the immediate inhibition of skin flare.

The immediate analgesic effect of the hormones was more pronounced than that of any other substance tested.

No significant differences in effect were found between the two hormones.

Tested for their later analgesic properties cortisone and hydrocortisone show some analgesic properties, but they are inferior to procaine hydrochloride and concentrated chlorprophenpyridamine (Chlor-Trimeton).

In the immediate inhibition of skin flare the antihistaminics show as much effect as the two hormones, while procaine hydrochloride has no immediate effect.

Possible explanations of these findings are discussed.

REFERENCES

1. Benjamin, F. B.; Cornbleet, T., and Grossman, M. L.: The Effect of Intradermal Injection of Adreno-Cortical Hormones, J. Invest. Dermat. **19**:109-119, 1952.

2. Goldman, L.; O'Hara, H., and Baskett, J.: A Study of the Local Reactions in Man to Cortisone and Compound F, J. Invest. Dermat. **20**:271-283, 1953.

3. Goldman, L.; Emura, E., and Baskett, J.: A Free Alcohol of Compound F of a Rod Crystal Type Producing a Local Inhibitory Reaction, J. Invest. Dermat. **20**:247-248, 1953.

4. Goldman, L.; Thomson, R. G., and Trice, E. R.: Cortisone Acetate in Skin Diseases, A. M. A. Arch. Dermat. & Syph. **65**:177-186, 1952.

5. Goldman, L.; Preston, R.; Rockwell, E., and Baskett, J.: The Inhibition of the Tuberculin Reaction and the Tuberculin Type of Inflammatory Response in the Skin by the Local Injection of Compound F, J. A. M. A. **150**:30-31, 1952.

6. Loew, E. R.: Pharmacology of Antihistaminic Compounds, Physiol. Rev. **27**:542-573, 1947.

7. Menkin, V.: Mechanism of Suppression of Inflammation by Compound F, Fed. Proc. **12**:98, 1953.

REVIEW AND APPRAISAL OF PRESENT KNOWLEDGE CONCERNING LUPUS ERYTHEMATOSUS

HENRY E. MICHELSON, M.D.
MINNEAPOLIS

IT WOULD require a remarkable gift for imparting knowledge to be able to report briefly everything that has been learned and everything that has been said about the many intricacies of lupus erythematosus. I fear that in the past glib terms have glossed over ignorance, or at best superficial knowledge of some of the processes that underlie the pathogenesis of this protean disease. This tendency is exemplified by the careless use of such terms as "collagen disease" and "fibrinoid degeneration" and by explaining away a finding, the cause of which is obscure, by aligning it with an allergic manifestation.

Historically, knowledge about lupus erythematosus has been acquired by the shrewd observations of clinicians and the interest of pathologists. The morphology of the skin lesions was soon learned, the symptoms of the disease and the cruder laboratory findings have been observed with monotonous regularity, but the real advances have come from the pathologists skilled in the newer tinctorial methods and from the cytochemists. Tribute must be paid to Klemperer and those whom he has inspired, such as Gueft, for to them dermatologists are indebted for investigations that are disclosing the basic pathologic disturbances which may turn in the right direction the search for discovery of the etiology of this baffling disease.

Donovan,[1] in his masterful address "Concepts of Disease Mechanisms," states, in part, that in the logical study of any disease we first attempt to identify the characteristic symptoms and signs. Next, we try to correlate these with the pathologic or biochemical changes and, if possible, express them in terms of altered physiology. Then, we try to identify the predisposing or causative factors. Lastly we try to learn how the disease process develops and why particular symptoms appear. In respect to lupus erythematosus many investigators have attempted to study all these facets, with the result that the morphology and symptomatology of the various types of the disease are now well documented, but a great deal remains to be learned.

Proficiency in diagnosis was greatly accelerated by discovery of the lupus erythematosus cell, and treatment of the disease has been entirely revised with the advent of steroid therapy. It becomes the duty of those who deal extensively with

From the Division of Dermatology, University of Minnesota; Henry E. Michelson, M.D., Professor and Director.

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patients who are the victims of lupus erythematosus to keep the profession informed of the knowledge they gain from day-to-day contact with such patients and, if possible, to outline new treatments as they are now evolved.

As is well known, there are two distinct clinical types of lupus erythematosus. The one is essentially a skin lesion; this type is called the chronic or discoid. The other is a severe systemic disease and is designated as the acute form. Between the two definite types are many gradations to which the term subacute lupus erythematosus has been applied. To this group have been assigned patients with numerous or widely disseminated skin lesions, also patients whose skin lesions have shown inflammatory activity, and patients who, in addition to skin lesions, had mild but persistent constitutional symptoms. It is difficult to classify some of these intermediate cases. A classification based on morphology is impossible, and at present no formula has been devised by which one may either ascertain the severity or predict the prognosis of the systemic cases. The extent of involvement and the number of lesions as well as their localization assist in evaluating the localized type, but a single lesion may be more resistant to treatment than numerous small lesions. Nodular or verrucose lesions do not signify a more severe process than do plane lesions.

The important question about a case of chronic discoid lupus erythematosus concerns the possibility of its transition to a systemic form. There is no way of estimating this possibility. That it exists is certain, but in my experience such a transition is extremely rare and hardly needs to be considered. When it has been reported, various explanations have been offered, such as a serious operation, overexposure to sunlight, frostbite, and so forth, but numerous patients with the chronic discoid form of the disease have undergone such insults without any untoward reaction. The reasons for transition to acuity, as the change is often called, are simply not known.

Patients who have so-called subacute lupus erythematosus usually have some mild constitutional symptoms and constitute a class who require not only watching but education so that they may protect themselves as much as possible from events which may precipitate trouble. This largely means conservation of strength and early bed care of trivial illnesses of the influenza type. Searches for the L. E. cell in such patients almost invariably result in negative findings. The cell is an indication of systemic derangement and does not develop beforehand to act as a beacon light.

There is no way that I know of classifying the subacute type. Obviously the character of the skin lesions and the severity of the systemic findings are guides. I believe in more severe cases it is safer, when in doubt, to take the more dismal view and expect an increase in symptoms rather than to be overly optimistic and predict improvement.

Classification of the systemic cases requires a careful evaluation of many factors and facts. A most detailed prodromal history, evaluation of the presenting symptoms, and a gradation of all the findings, clinical as well as blood and urine analyses, are an aid, but foremost is a general evaluation of the patient. This will be discussed in more detail later.

Numerical frequence of L. E. cells (following a prescribed technique for determining this) has been proposed as a measure of severity. At the present time I would be inclined to accept the importance of the finding of a large number of cells,

to a certain extent, but I have seen patients in whom the cells were absent and yet whose course was very severe and downward. Therefore a numerical estimate of L. E. cells alone cannot be an infallible guide. As more knowledge of the L. E. phenomenon is acquired, degrees of severity may possibly be estimated from the behavior of the clumping and the character and number of the cells, but at present I do not believe it would be safe to advocate reliance on this procedure alone. The value of the test is diagnostic and not prognostic.

Classification or gradation of patients with lupus erythematosus is at present on a clinical basis and therefore somewhat arbitrary. The strictly localized or chronic discoid type and the systemic type, with an acutely ill patient, are readily identified, while the intermediary cases will be aligned with either extreme, depending upon the correlative findings.

Almost all articles dealing with the subject begin by stating that lupus erythematosus is a disease of unknown cause. Few authors even speculate about the etiology, and research along this line has not occupied much attention of late. Historically lupus erythematosus was considered to be a form of lupus vulgaris, and even today some continental dermatologists insist that tuberculosis plays a role in the production of lupus erythematosus. The histology of chronic discoid lupus erythematosus does not in any way suggest a tuberculous etiology. Acute disseminated miliary tuberculosis has been found at autopsy in enough patients who apparently succumbed to acute systemic lupus erythematosus to keep alive the concept that a variety of antigens may produce the morphologic pattern which is called lupus erythematosus.

Rost [2] in 1949 expounded the theory that lupus erythematosus was a rheumatoid disease based on allergy to an infection. He believed that patients with the disease had an allergic predisposition acquired through one or several infections during early life which sensitized the mesenchymal tissue so that subsequent trauma (in the widest sense) would provoke an allergic reaction in some organ; for example, the skin. This would manifest itself as a serous inflammation, which he states Rössle considers to be a typical allergic reaction, characterized by interstitial exudation, disruption of the histologic pattern of various tissues, histiocytic degeneration, and even histolysis.

In contrast to ordinary suppurative inflammation, the serous form produces no pus. Except in severe cases the tissue returns to normal without any or very slight scar formation. Serous inflammation is usually mild but may be violent with hemorrhages and necrosis. Rost points out that "rheumatic complaints" are common, especially in the prodromal stage of acute lupus erythematosus, and he claims these are based on serous inflammation in the joints, muscles, kidney, heart, and small blood vessels. He admits, however, that proof is still missing that lupus erythematosus is closely related to and should be grouped with erythema multiforme, rheumatic purpura, erythema nodosum, and periarteritis nodosa, but he believes that the evidence points strongly to a similar pathogenesis based on allergy caused by an infection.

Rost's paper contains reasonable deductions, and I am impressed with his references and remarks concerning serous inflammation, but the assumption that the pathogenesis of lupus erythematosus can be explained on the basis of an allergic reaction must be subjected to critical analysis and experimental studies. This has been done by Gueft and will be discussed later.

Gold,[3] in a recent (1953) clear exposition, defends the thesis that all forms of lupus erythematosus have a common pathogenesis based on the response to a number of precipitating causes, and that patients who have the localized type maintain a systemic immunity or resistance, while in those who have systemic lupus erythematosus, there is a disturbance of the immune mechanism which is dependent upon the functions of the pituitary-adrenal axis. He explains the production of lesions and symptoms on the basis of this hypothesis and discusses endocrine imbalance and other factors which may well account for the production of the well-known symptoms and findings in this disease. I am unable to refute Gold's deductions concerning the production of the clinical syndrome called lupus erythematosus, but I doubt a multiple etiology because of the consistency of the findings in so many patients with this disease. It seems to me that such a uniform picture, even if varying in intensity, must have a single cause.

There are, to be sure, other articles speculating on the causes of lupus erythematosus, but so far as I know no recent work has been reported revealing findings which may indicate a specific cause.

The histology of cutaneous lupus erythematosus is fairly well established; however, cytochemical changes must be studied, for the older methods do not adequately reveal the nature of extracellular changes. Dermatopathologists have made painstaking microscopic analyses of skin specimens in all types of lupus erythematosus, but biochemical and biophysical methods have not been applied; hence the general pathologic changes in the internal tissues and organs, which have been studied by Klemperer and his pupils, have revolutionized previous knowledge. One hesitates to describe the cutaneous pathologic changes without having the results of studies made on skin biopsy material for evidences of disturbances of nucleic acid and nucleoprotein metabolism as demonstrated by identifying free hematoxylin bodies. If and when such studies are made, I feel certain it will be possible to correlate the internal and cutaneous pathology much better than it can be done today.

Histopathology of the skin in lupus erythematosus has nevertheless been of great value in diagnosis and also in explaining the morphology of the lesions on a histologic basis. Newer studies will of course utilize the knowledge now accumulated. Without describing in detail the well-known histologic changes, I should like to call particular attention to the edema, which in the microscopic sections I have examined is a constant and striking feature of the disease but not a permanent one. Hence it may not be seen in material excised after the lesion has become well established. It is noted particularly in the early erythematous stage of a lesion, when the edema may be seen throughout the cutis, and has a decided effect on the collagen, which either appears drenched or broken into fragments. At this stage there is a minimal amount of infiltrate, sparsely scattered about the blood vessels. Later on the infiltrate becomes so dense that other changes are masked. I am impressed with the importance of this finding because I believe that edema represents a powerful response to a toxic influence, and that in lesions destined to become the chronic discoid type the toxic influence is partially overcome and infiltration occurs; whereas in patients who have the acute systemic form of lupus erythematosus, the skin lesions represent the early phase of the chronic type, the toxic influence predominates, and much less infiltration takes place. Since the edematous stage of the discoid type and the early findings in a skin lesion from a patient with acute systemic lupus

erythematosus are identical in many instances, it seems reasonable that the two conditions may be different manifestations of the same disease.

Dermatopathologists are able to make a diagnosis of lupus erythematosus with reasonable assurance from a skin biopsy, but it is a diagnosis based on an over-all evaluation of the case and not on a specific finding. It must be emphasized also that there is a decided variation in different sections. The differential diagnosis in clear cases is not very difficult, for few dermatologic lesions histologically resemble lupus erythematosus. However, seborrheic keratoses, lichen planus, and the so-called lupus erythematosus-like actinic dermatitis may be very difficult to differentiate from lupus erythematosus. In fact, at times it is impossible to make a conclusive diagnosis. I have also seen sections of erysipelas which were surprisingly similar to some seen in acute lupus erythematosus.

The doubts about differential diagnosis which I have experienced emphasize the need for studies on the presence of hematoxylin bodies in skin sections from lupus erythematosus. If they could be found in a high percentage of cases, their presence would be a valuable factor in making or excluding a diagnosis of the disease. Dr. Gueft kindly examined for me cutaneous biopsy specimens from 30 cases of various forms of lupus erythematosus and informally reported finding hematoxylin bodies in 50% of the sections. Further investigations along this line are necessary. I am now undertaking such a study, which will be reported in due course.

The work of Klemperer and those associated with him has opened an entirely new vista to the internal pathology of the systemic form of the disease. It is not necessary to review the work of Gross, Ginzler and Fox, and others. All students of lupus erythematosus are familiar with the emphasis on the collagen and the finding of the so-called hematoxylin bodies and how, by cytochemical means, these bodies were shown to contain partially depolymerized desoxyribose nucleic acid. The concept of fibrinoid in the acute type was studied and Gueft [4] stated that vascular fibrinoid in acute lupus erythematosus is one of the products of the unusual disturbance of nucleic acid and nucleoprotein metabolism which was found to be specific for this disease. Since he did not find hematoxylin bodies in the organs of patients who died of periarteritis and allergic granulonephritis, diseases assumed to have an allergic background, he concluded it was unwarranted to group the fibrinoid of lupus erythematosus with the fibrinoid of the other two diseases. He challenged the assumption that fibrinoid denotes only allergy or hypersensitivity. Such refined work can be evaluated only by highly specialized workers, but all must agree that this is the type of proof one is looking for rather than rationalized deductions on the assumption that lupus erythematosus is an allergic disease. Gueft and Laufer,[5] in a paper which appeared in the *A. M. A. Archives of Pathology*, reported further studies on the cytochemistry of disseminated lupus erythematosus and I am deeply indebted to Dr. Gueft for the privilege of quoting from it.

The general pathology of systemic lupus erythematosus has been given a great deal of attention in the past decade. Prior to the studies of Klemperer and his associates, the observations of Libman and Sacks represented the only contribution which was significant, and even they did not diagnose the type of endocarditis which they described as being a part of acute lupus erythematosus.

The concept of collagen and other alterations in lupus erythematosus as expounded by Klemperer and his associates need not be reviewed; suffice it to

say that their studies proved that the systemic form was a diffuse and an organic disease, and that the pathologic changes in all of the involved tissues was essentially the same. At first the anatomic criteria that they applied to the acute form provided only a descriptive characterization of the disease, but they were not satisfied with that, and their studies have been continued, so now more insight has been gained, and in the most recent article by Gueft and Laufer [8] there is much more concrete evidence of a specific nature which reveals some of the basic principles underlying the pathogenesis of systemic lupus erythematosus. The article should be studied in its entirety, for the information I am able to give here is merely a very brief abstract. The study was based on 14 cases of lupus erythematosus which came to autopsy, and the detection of hematoxylin bodies was the particular object of investigation.

I believe it should be of particular interest to internists and pathologists to quote directly their report of the microscopic findings at autopsy. "There was involvement of all serosal membranes in four, of pericardium and pleura in one, of pericardium and peritoneum in one, of pleura and peritoneum in three, and of pleura or peritoneum in one case respectively. The serosal involvement was characterized by fibrous adhesions in six cases; these fibrous adhesions showed a conspicuous gelatinous appearance. Enlargement of the heart, with weights over 300 gm., was found in nine cases, four of which had subacute glomerulonephritis. Endocardial vegetations were observed in five cases, four of which were seen on the auricular and ventricular surfaces of the valves and one on the mural endocardium. These fulfilled the criteria for Libman-Sacks atypical endocarditis. Generalized lymph-node enlargement of moderate to striking degree was observed in all cases except one. In four of these, areas suggestive of necrosis were noted, and the necrosis was verified by histological examination. Skin lesions of erythematous nature were noted in five cases, one of which showed petechial hemorrhages including the palm of one hand. In view of the experience that mild cutaneous rashes fade after death, it might be added that every one of the patients showed some erythematous lesions during the period of observation. Mucous membrane lesions of inflammatory, mostly ulcerative, character were seen in four cases. Splenic enlargement was observed three times, with weights of 270, 560, and 780 gm. In one case a slightly enlarged spleen weighing 160 gm. had been removed two years prior to death because of the clinical diagnosis of thrombocytopenic purpura. Decubital ulcers were present in four instances. The brain, examined in five cases, showed edema once."

The microscopic findings were the same as previously reported, but it is interesting to note that wire-loop glomeruli were present in every instance, and that hematoxylin bodies were found in all but one of the cases, not limited but widely distributed. Kidneys, lymph nodes, ovaries, and heart were the most frequently affected. The hematoxylin bodies were also found in the striated muscle in four cases.

The chief purpose of Gueft and Laufer's report was to reevaluate the validity of hematoxylin bodies as a specific criterion for the autopsy diagnosis of systemic lupus erythematosus. Having found such bodies in various tissues in 13 of the 14 cases, they then studied 30 control cases and concluded that free hematoxylin bodies are found only in systemic lupus erythematosus, and therefore constitute a reliable criterion for diagnosis. Their extensive physical and chemical studies of the hematoxylin bodies showed evidence of a progressive degradation of the desoxyribose nucleic acid of the nucleoprotein of the hematoxylin bodies and ultimate complete

disappearance of the nucleic acid molecule. They also stated that the fibrinoid material in systemic lupus erythematosus is mainly made up of a protein residue of nucleic origin.

I have quoted extensively from this work because I believe it is the latest knowledge on the subject and should be very valuable in interpreting the pathogenesis of systemic lupus erythematosus.

One query that comes to my mind is: Were the macroscopic and microscopic findings in these fourteen cases sufficient in themselves to cause the death of the patients? There is no question about the great diffusion of involvement, but on the other hand, were the pathologic changes in the vital organs, such as the kidneys or the heart, sufficient to be the cause of death? If the answer is "no," and I believe it would be, it emphasizes what we have often observed, namely, that the decline and ultimate death of patients with systemic lupus erythematosus does not seem to be caused by the failure of any particular organ. Even in patients with marked clinical kidney impairment, a frank uremic state does not often develop.

I believe that the diffuse pathologic changes, the serosal lesions, and the general decline of the patient without definite focal symptoms and pathologic changes, uphold the old impression of the "toxic" nature of systemic lupus erythematosus. Another observation which somewhat corroborates this is the complete lack of complications in the systemic form of the disease. A frank complication is rarely encountered. In one of our patients a large subsoleus abscess developed, and in three others thrombophlebitis, but aside from those I recall no other complications which could not be interpreted as part of the syndrome.

The symptomatology of discoid lupus erythematosus need not be discussed. The visual presence of the lesion is the chief complaint. Persistence of the lesion despite treatment causes apprehension, but there are practically no subjective symptoms. I have already mentioned that there is some degree of light sensitivity, complained of by most of the patients, but aside from some burning sensations and redness in the early spring, almost all patients with chronic discoid lupus erythematosus do not and need not avoid outdoor activities.

The very diffuse nature of the pathologic changes in systemic lupus erythematosus accounts for the great variation of the symptoms and signs. In fact, the signs and symptoms cannot be outlined, but the importance of the status of the patient as a whole must be stressed. Patients with the acute systemic form of the disease are generally sick. They rarely complain of any particular pain. The symptoms may or may not point to certain organ involvement, as, for example, anorexia and abdominal pain to peritoneal inflammation, painful breathing to pleural irritation, or dyspnea to pericardial involvement. The over-all picture is that of a prostrate patient, restless, extremely uncomfortable. The skin is dry and hot, obviously from high fever. The lips are parched, cracked, and if specifically involved, either are eroded, bleeding, or covered with bloody crusts. The tongue is extremely dry. If there are lesions on the face, they may vary from a dusky erythema to blisters and may involve the forehead, usually stopping abruptly at the hairline. The sides of the neck and the "V" of the chest often have more discrete lesions which are crusted. A scaling or crusted macular eruption is often present on the arms and the dorsa of the hands, while diffuse erythematous or petechial lesions are common on the palmar side. The trunk is usually free from eruption but a generalized measles-like

eruption or even purpuric eruption is occasionally seen. Lesions from the knee down are often purpuric. Edema of the face, especially of the lower eyelids, is common and to me, when marked, it is a good indication of severity. Before the advent of steroid therapy this symptom was persistent. In patients who respond to steroids, and most do, at least initially the facial edema disappears very rapidly.

The course of acute disseminated lupus erythematosus, before the advent of steroid treatment, was fairly uniform. Following severe onset, the patient continued to remain very ill, with the addition of few new symptoms. The fever remained high; the eruption usually subsided somewhat; edema became firmer, and the skin often assumed a dusky bluish tinge, either due to a degree of cyanosis or to a mild purpura. In a few patients the skin became sepia-colored, the pigmentation continued, and if the case was prolonged, the color became very dark, resembling a severe chloasma. In the acute cases, edema of the legs rarely developed to any marked degree. Occasionally the legs showed large purpuric areas. Severe, rapid loss of weight, not before, but concomitant with the febrile attack, seemed to me to be an important sign and has been noted more recently in patients whose other symptoms have been controlled by steroid therapy.

Death in the acute form of lupus erythematosus did not occur in a few days. The course, to be sure, varied somewhat, but the patients gradually lost ground, there being a change of accent on certain symptoms from day to day. The patients were usually clear mentally, but occasionally severe cerebral symptoms developed, and I recall two attempted suicides and one successful suicide. Severe psychosis requiring restraint was seen occasionally. The character of the illness changed from the acute septic appearance at onset to a more profound toxic state, and termination in a large percentage of the patients was in from one to three months. A few patients survived longer but remained bedridden, and a subsequent severe febrile attack with death was to be expected and usually occurred.

This has been a very brief description of acute disseminated lupus erythematosus, as it is known to dermatologists, but the current literature deals largely with what is known as and called systemic lupus erythematosus. This type has no classic picture and concerns patients who often have histories of prolonged, rather mild illnesses which gradually became more severe, or a period of acuity emphasized the previous complaints. The known number of such cases has greatly increased with the use of L. E. cell tests, for these cases formerly could not be diagnosed accurately, especially if there were no cutaneous lesions. However, before Hargraves' discovery there had been an awakening to the possibility of the inclusiveness of the term systemic lupus erythematosus.

It is hardly necessary to reiterate the many presenting symptoms of the systemic form. However, I should like to emphasize some points, and in order to do so I reviewed the charts of the last 40 patients admitted to the University of Minnesota Hospitals upon whom a diagnosis of lupus erythematosus had been made. Various types of the disease were represented, but no patient was admitted who did not have systemic symptoms. After the data were carefully analyzed, the impression that not a great deal could be learned about lupus erythematosus from the symptomatology, regardless of presenting symptoms or localized signs, was verified. Actual information about the probable course of severe systemic lupus erythematosus must be obtained from the knowledge that dermatologists have gained in handling patients

who had acute disseminated lupus erythematosus, for in this form of the disease most of the symptoms seen in the more protracted and less severe forms are seen at their worst. One also learned to have great respect for the possibilities of this potentially lethal disease and not to be misled by temporary amelioration of symptoms.

I hope it is not impertinent to warn those who have more recently been initiated into the group who care for lupus erythematosus patients that the disease is still a clinical one, and that, while laboratory procedures have great diagnostic value, the most scrupulous observation of the patient is necessary in order not to be misled by improvements in laboratory findings.

I should like to make a few remarks about symptoms which are commonly associated with systemic lupus erythematosus.

Fever is a common accompaniment of the disease. (From experience with the acute septic type, hyperpyrexia is expected.) In the more protracted types, however, the fever is rarely high. In reviewing the 40 cases mentioned previously I was surprised to find how often the temperatures did not rise above 99 or 100 F. Therapy, of course, had an effect, but even before therapy low-grade fever was common. In many patients with chronic discoid lupus erythematosus, if the temperature is taken twice daily, it will be found that there is a constant elevation of one or two degrees. Fever in itself is more important in its persistence than in its range.

I have mentioned loss of weight and how difficult it is to bring about a gain in weight, in spite of treatment, when other symptoms of the disease persist. I believe it is important to keep an accurate chart of the weight. Arthralgia, myalgia, and even arthritis are very common symptoms; in fact, there are few patients who do not complain of such symptoms; however there is not much debility because of them. I have seen frank lupus erythematosus of various kinds develop in patients who have had rheumatoid arthritis for years. I do not know if this is significant.

Symptoms referable to the heart, pleura, lungs, and peritoneum are often noted. Such symptoms are nearly always vague but persistent. They are hard to evaluate, and if the case should end fatally an anatomic explanation is often lacking. I have noted this a number of times, particularly when the patient had complained of difficult and painful breathing. The most frequent symptom referable to the gastrointestinal tract is diarrhea which has been a presenting symptom in the protracted type of the disease often enough to advise an L. E. test in patients with chronic unexplained diarrhea.

Many authors report generalized adenopathy as being a common finding. That has not been my experience, but my searches for this finding in the past may not have been adequate. Raynaud's phenomenon, both historically and as an accompaniment of the disease, is quite common. I have recently seen two patients upon whom an initial diagnosis of Raynaud's disease had been made. They also had peculiar blue macules on the cheeks. When these macules were examined histologically they showed numerous enlarged superficial vessels. Since the patients complained of marked fatigue and loss of weight, a search for L. E. cells was made. Since the tests were positive, it lead us to the conviction that Raynaud's phenomenon, especially if accompanied with constitutional symptoms, could be part of the systemic lupus erythematosus syndrome.

Blood changes in systemic lupus erythematosus have been assiduously studied. Leucopenia has been so frequently mentioned, I was surprised to find that only 30%

of the patients had leucopenia, most of the white blood cell counts ranging from 3,000 to 5,000, while severe leucopenia of from 1,000 to 2,000 white cells per milliliter were rare. Infections such as bronchitis usually raised the count. There was usually a reduction of hemoglobin and a little less often a reduction in erythocytes. Thrombocytopenia and purpura have often been reported. A point that has not been stressed enough, I believe, is the danger of transfusing with whole blood patients who have severe lupus erythematosus. They are prone to hemoagglutinins or to have severe inexplicable reactions. In two such instances I have seen death ensue a few days after transfusion, presumably due to transfusion reaction. Small amounts of blood given for two or three days in succession and not repeated have been advised. I tried this on one patient with no reaction but also without improvement in the anemia. The blood sedimentation rate is almost always elevated and remains so even in patients who respond well to steroid therapy.

Neurologic symptoms, such as polyneuritis and localized neuritic pain, are noted occasionally and may even be a presenting symptom. Psychic symptoms, such as extreme anxiety, depressed states, even frank psychosis all have been reported. We have encountered all of these occasionally but usually in patients who have been ill for some time and not as initial symptoms. Since the advent of steroid therapy, psychic changes have been noted more frequently and their cause is then not easy to ascertain, because even if the drug is withdrawn the symptoms continue. Psychiatric consultation should by all means be insisted upon in such instances; the safety of the patient depends upon it. In our hospital such patients are immediately transferred to the neuropsychiatry department.

During the past two years, electroencephalographic studies have been carried out on seven patients with lupus erythematosus who demonstrated either psychic or neurologic findings. The results were normal in all cases. This group included one female patient for whom electroencephalographic findings were normal during a phase of subacute systemic activity and at the height of a violent psychotic episode which followed steroid therapy.

In describing some of the symptoms encountered in patients with systemic lupus erythematosus, I have stressed the variations which I believed were somewhat unique. The classic symptoms are so well known and have been so often described that I have not discussed them.

Laboratory findings, such as falsely positive results on serologic tests for syphilis, results of urinalyses, and others also have been adequately discussed, and in the past five years there have been a great many papers from many countries, dealing with the L. E. phenomenon and the L. E. cell. I cannot add anything new to this, but I would like to stress the need for caution in accepting reports on the presence of the L. E. cell unless those who make the test have been properly trained, for errors both in technique and in interpretation can easily be made.

Weizsäcker [6] in "Der kranke Mensch" says, "A patient is not only a "case" but also a person, a member of a family, of an income group, having a background that is part of him as much as he is part of it." With this in mind I reviewed as best I could from the scant data on the records, the backgrounds of some 600 patients with lupus erythematosus of all types. Most of them were of the lower middle class, men and women who worked hard for a living, farmers and their wives, truck drivers, artisans, and the like. In the group there was only one doctor. There were two doctors' wives (one had the severe subacute type). There were only two women

university students (both died of the acute septic form of the disease). There were only two student nurses, one of whom succumbed. There were very few of university education level, and there were none with acute lupus erythematosus who belonged to the so-called society group. This, I believe, is worthy of note because such people as a rule expose themselves to excessive amounts of sunlight and continue their indulgence in the winter months by sojourning in sunny climes. Prolonged exposure of large parts of the body to the sun's rays certainly cannot play much of a role in the production of lupus erythematosus.

The incidence of lupus erythematosus is not great, probably because of a high degree of resistance or immunity. If a latent infection exists, environmental and economic factors may be important. If the infector is a virus, one cannot draw analogies from other virus disease, such as varicella or poliomyelitis which affect all classes of society alike and very often several members of the same family. Familial occurrences have been recorded in lupus erythematosus, but they are rare.

Why then does lupus erythematosus occur in this rather ill-defined group, or rather why does it so rarely occur in a more privileged group? Nutrition, fatigue, states of anxiety, and stress readily come to mind, but one hastily dismisses them because, of the millions who live harried lives, a very small percentage develop lupus erythematosus.

I believe it is important to take into consideration the economic or social level of patients with lupus erythematosus, so that accurate statistics may be accumulated. One is at once reminded of the high incidence of lupus vulgaris in peasants in certain geographic areas of Europe. In that disease the economic level and the geographic location are definite factors in the incidence.

Exact geographic surveys of lupus erythematosus should also be made in the United States. Marchionini's [7] studies revealed that it is a disease of temperate zones. An accurate epidemiologic survey might be revealing.

The treatment of lupus erythematosus may be divided into four parts; namely, that for (1) the chronic discoid type, (2) the so-called subacute cases, (3) the acute septic type of the systemic disease, and (4) the protracted systemic type.

The treatment of chronic discoid lupus erythematosus is directed against the lesion with the object of obliterating it if possible. This has been attempted by a variety of locally applied agents, none of which have been entirely satisfactory. Since the process results in a scar, it must be emphasized that local treatment does not prevent scarring and may even accentuate it. Freezing the lesion with solid carbon dioxide is the best local remedy in my experience, and I know of no other method which equals it.

A great many drugs administered internally have been tried, but none were outstandingly successful. I gave up the use of bismuth and gold salts because the results did not warrant the long-continued use that was necessary to achieve the indifferent results, nor did their use prevent new lesions from occurring.

Quinacrine (Atabrine) has gained favor in the last few years. It is given by mouth. There is no question that the drug favorably influences and at times brings about a disappearance of cutaneous lesions. I believe quinacrine is the drug of choice at the moment for chronic discoid lupus erythematosus, but it must not be looked upon as a specific, for in some patients the results are temporary, in others no effect at all is seen, and it does not prevent recurrences. Details of its use have

been adequately reported by others. I have administered quinacrine to patients with subacute lupus erythematosus who had low-grade fever and prostration. The patients bore the drug well, and in a few the response merited its use. I have also given quinacrine to patients with systemic lupus erythematosus, either acute or protracted, who had become afebrile and reached a stationary position in progress on a regimen of steroid therapy, but there was no immediate effect. This led me to believe that quinacrine should not be used as an adjuvant to steroid therapy in the systemic form of the disease. I have not shared the unbounded enthusiasm of some concerning quinacrine. Until a better drug is discovered, I believe it should be tried in the chronic discoid form and in some cases of subacute lupus erythematosus. In severely ill patients with systemic lupus erythematosus, time cannot be wasted in giving it a trial before the use of steroids. Its precise position in the therapy of lupus erythematosus cannot be fixed until it has been in use for at least five years.

The treatment of subacute lupus erythematosus requires personal judgment. Methods for handling patients with the chronic discoid type may be advocated empirically with relative safety, but patients who have extensive progressive eruptions or who have persistent accompanying constitutional symptoms require individual evaluation, which of necessity will depend upon the interpretation of the case by the physician in charge. I believe one may, without fear of criticism, recommend that consultation with a dermatologist experienced in treating such cases is advisable. When such patients come into my hands, I insist on hospitalization for study which includes, besides a general examination, careful observation of the temperature curve, urinalyses, L. E. cell tests, and above all, noting how the patient and the eruption behave when at rest. A few days in the hospital often bring about a decided change, which then permits trial of quinacrine therapy; on the other hand no change or an increase in symptoms calls for longer observation and evaluation. If tests are positive for the presence of the L. E. cell, the question of steroid therapy must be met. It is my conviction that steroids should not be given to patients with subacute or mild systemic lupus erythematosus unless they take a turn for the worse. This will usually be evidenced by a protracted elevation of temperature. Persistent marked fatigue bordering on prostration may also be an indication for a trial of steroid therapy. There are other indications but they merely emphasize the need of individualization. Steroids should not be administered in small doses to such patients prophylactically. They neither cure the disease nor prevent future exacerbations. The number of patients who fall into the group just mentioned is increasing because of renewed interest in lupus erythematosus. In this group are encountered some of the most baffling therapeutic problems. I can only again warn against indiscriminate steroid administration and urge evaluation of each patient, and remind physicians that response from rest and supportative measures are much to be preferred to an effort to establish a so-called maintenance drug treatment.

The treatment of acute or severe systemic lupus erythematosus is likewise difficult. There are two classes of such patients: first, those with an initial acute, septic type of illness, and second, those who have had mild or moderately severe lupus erythematosus whose condition suddenly becomes much worse.

The immediate treatment of the two classes is about the same. There is no doubt that at the present time steroids must be used in acutely ill patients. The initial dosage is regulated by the severity of the case and it is regulated by the response.

I shall not dwell on choice of drug or method of administration. In severe cases I do not hesitate to give large initial doses and to increase them if necessary. If the response is satisfactory, I do not hesitate to reduce the dosage; it can be increased again if necessary. The temperature and general condition of the patient are the best criteria for judging this. Anemia, leucopenia, and albuminuria are not contraindications to high dosage, nor is lack of improvement in such conditions any reason for stopping the use of steroids. The fever, eruption, edema, prostration, and general discomfort improve when the treatment is successful, although the laboratory findings may not change or only improve slowly. Albuminuria and the blood sedimentation rate often do not change at all under steroid therapy. Anemia and leucopenia gradually improve in favorable cases.

We decrease the dosage of steroids to a minimum as soon as permissible, and completely withdraw the drug if a reasonable trial has not been successful or if a particular symptom, such as a psychic one, persists or increases under its use, or if a new symptom develops which might be attributed to the drug. The ill effects of the steroids have been so thoroughly described that I shall not review them. The so-called maintenance dosage of steroids in patients who have survived a severe attack is based on the observation that if the drug is entirely withdrawn symptoms recur. It is also administered to patients who, when the drug is withdrawn, are invalided.

The problem of maintenance dosage is a very difficult one. In those patients who immediately become severely ill without adequate daily doses there is not so much doubt, but it must be mentioned that in that group the so-called maintenance dosage merely keeps them from being severely ill. They have not been returned to full health by initial high dosage and then kept there by a certain daily dose. On the contrary, they are moderately sick people who are kept from being dangerously sick by this continued treatment.

The other group for whom maintenance dosage is used are those who have recovered either from an acute phase or from severe systemic symptoms and can be kept in a state of moderate well-being only by a certain daily dose of a steroid. These patients also are as a rule semi-invalids, even with the maintenance dosage. Since the diagnosis of systemic lupus erythematosus is so inclusive, it can readily be seen how some patients whose illness was not very severe may be restored to a reasonable state of health, but those patients who have severe systemic or acute septic lupus erythematosus, in my experience, have not made the splendid recoveries and return to complete health reported by some authors. In fact, I am far from encouraged about the ultimate state of these patients. There is no doubt about the value of the steroids, but I cannot too strongly emphasize that they are not a specific for lupus erythematosus. The steroids obtund the intensity of systemic lupus erythematosus, but apparently they do not raise resistance or produce immunity. A more specific therapy would be most acceptable. Supplementary therapy with antibiotics and other measures for particular exigencies are of course used.

The treatment of severe or acute systemic lupus erythematosus is most difficult, and, if the patient survives the acute or severe period, prolonged after-care with or without maintenance dosage of steroids must be expected. Complete restoration to health is the exception and by no means the rule.

COMMENT

I have attempted to present the highlights of the present-day knowledge about lupus erythematosus. It does not require a long association with the disease to realize that the name has been applied to a variety of conditions which at first thought seem to have little in common, but one soon realizes that the inclusiveness of the term is justified by the pathologic and other findings.

The knowledge about chronic discoid lupus erythematosus has not changed very much since this type was first described. However, a thorough knowledge of cutaneous lesions, the recognition of their great variation, and especially the observations which suggested that the chronic lesion in its early state was identified, both clinically and microscopically, with those cutaneous lesions noted by early dermatologists in acutely ill patients and diagnosed as acute disseminated lupus erythematosus, served as the foundation for the present-day broad concept of systemic lupus erythematosus. One must not lose sight of these pioneer observations, for even today the classic acute cases furnish the material for investigations and advances. In spite of the more recent reliance upon laboratory tests for diagnosis, the true acute cases can be diagnosed by dermatologists with a very high degree of accuracy, thus furnishing investigators with indubitable material.

Patients who have no skin lesions, even though the presence of L. E. cells has been demonstrated, constitute a group which has attracted a great deal of attention, but much more time is necessary before the knowledge concerning them will be as complete as that which has been accumulated concerning patients with the acute septic type of the disease.

I believe one should stress the organs that may be the seats of the process in systemic lupus erythematosus rather than its symptomatology. When diagnosticians realize that the symptoms either may be a combination of manifestations of dysfunction of one or several organs, or may arise from the entire organism battling a devastating cause, their conception will not be that of a specific disease picture. Rather, they will acquire a feeling of awareness and will include systemic lupus erythematosus as a diagnostic possibility in patients who have most diverse presenting symptoms.

It must be mentioned that when the heart, the kidneys, or other organs are involved in systemic lupus erythematosus, the symptoms and findings relative to the particular organ are based on dysfunction of, or actual destructive alterations in that organ and can only be attributed to lupus erythematosus by implication when that diagnosis is made upon the patient as a whole and not upon the organ. For example, one cannot speak of lupus erythematosus nephritis, but must state that nephritis is present in a patient who has systemic lupus erythematosus. The diagnosis of systemic lupus erythematosus is made on the organism as a whole and not on the behavior of an organ.

Patients with subacute lupus erythematosus under the present classification always have skin lesions. Here again dermatologic diagnosis is satisfactory. But is there a subacute form of systemic lupus erythematosus? I believe there must be, for in many of the systemic cases there is a long prodromal history. Therefore, the mild systemic cases may be looked upon in much the same light as the subacute (cutaneous) type is at present. This suggests that the awareness, which is essential to diagnosing the severe systemic type, must be extended so that clinicians in the

future may learn the symptomatology of the incipiency of systemic lupus erythematosus. Should the cause be found and easily demonstrated, or should some diagnostic test be discovered, the early diagnosis will of course be simplified. Early diagnosis would mean early treatment, and I believe even with the therapeutic measures of today many patients then could be guided to recovery, for we have seen patients with prolonged and enforced stays in the hospital improve, while those who must leave or who insist upon leaving after a short stay do poorly. I believe if rest treatment could be instituted before the patient became debilitated, the prognosis would be much improved. This brings up the great need for public care for patients with severe systemic lupus erythematosus. Few of these patients have the means to be hospitalized for the long time that is necessary to bring about sufficient recovery to allow them to return to their homes where, even then, a long regimen of care will be necessary. Tuberculosis sanitaria would be well suited for this care if it could be made legally possible.

Lupus erythematosus should be and is the concern of the entire profession. Because of the nature of this disease, with its obscure or disguised symptoms, its diagnosis requires the talents of specially trained men. Those specialists who are particularly interested in the disease can contribute a great deal to each other's knowledge by maintaining a receptive and mutually respectful attitude.

REFERENCES

1. Donovan, D. K.: Concepts of Disease, Irish J. M. Sc., p. 137, April 1953.

2. Rost, G. A.: Erythematodes as a Rheumatoid Skin Disease, Med. Klin. **44**:1242 (Sept.) 1949.

3. Gold, S. C.: An Hypothesis Concerning the Pathogenesis of Systemic Lupus Erythematosus, Brit. J. Dermat. **65**:43 (Feb.) 1953.

4. Gueft, B., and Laufer, A.: The Concept of Fibrinoid in Acute Lupus Erythematous, Proc. New York Path. Soc., 1950-1951, p. 103.

5. Gueft, B., and Laufer, A.: Further Cytochemical Studies in Disseminated Lupus Erythematosus, A. M. A. Arch. Path. **57**:201 (March) 1954.

6. von Weizsäcker, V.: Der kranke Mensch, Stuttgart, A. F. Koehler, 1951, p. 453.

7. Marchionini, A.: Beziehungen der Klimatologie und Ethnologie zur Entstehung von Hautkrankheiten in Anatolien, Schweiz. med. Wchnschr. **74**:842, 1944.

NYLON AS A CAUSE OF DERMATITIS IN A PATIENT WITH VASOSPASTIC DISEASE

ROBERT G. CARNEY, M.D.
IOWA CITY

NYLON fabrics may be an important factor in the production and prolongation of skin diseases, notably in persons with vasospastic disease of the feet. Since very shortly after its release on the market, nylon has been implicated in the etiology of dermatoses because of sensitization of the skin to dyes and fabric finishes used in the manufacture of nylon garments. Search of the literature fails to reveal any report of skin disease caused by nylon itself. In my personal experience, lesions of "the pernio type" have been produced and reproduced by contact with nylon cloth, probably because of its lack of absorbency. It seems likely that nylon may also play a part in other dermatoses in which sweating, moisture, and maceration are involved.

REPORT OF CASE

R. G. C., a physician, aged 39, has developed swollen, painful heels late each fall since 1948. At least twice previously, probably in the winters of 1941-1942 and 1942-1943, similar lesions had developed but were relieved within a few days by the wearing of foam rubber pads between the plantar surface of the heels and the insoles of the shoes. The condition did not recur during three years of military service, nor for a year thereafter. When the recurrence appeared in 1948, no relief was obtained with the foam rubber pads. The heels at first became red and swollen and perspired excessively. As the affection progressed, white, dead-looking patches appeared (Fig. 1); these were tender on pressure and gave rise to constant burning sensations accentuated by prolonged light pressure of shoes or bed clothing.

Since December, 1945, Raynaud's phenomenon has been manifested in the fingers following chilling exposures, particularly when the patient was engaged in activities requiring the use of the hands for firm pressure or holding vibrating objects. Otherwise the general health has been excellent.

Attempts at therapy included foam rubber pads, frequent changes of socks and shoes, frequent bathing of the feet, the use of aluminum antiperspirants, and the wearing of light, perforated shoes. None of these measures were of appreciable benefit. With the advent of warm weather the condition would gradually disappear, only to recur about a month after cold weather began in the fall, and this pattern prevailed through 1949 and 1950.

In November, 1951, the affection began on schedule and reached an extremely uncomfortable state by the end of December. At that time all-nylon and nylon-reinforced hose were discarded, and all-cotton socks were worn exclusively. The subjective symptoms improved very quickly, and by the end of three weeks the whitened, tender areas had all but disappeared.

Beginning Feb. 7, 1952, all-cotton socks were worn on the right foot and cotton socks with nylon-reinforced toes and heels on the left. Within a few days the symptoms of burning and of pain on pressure returned in the left heel only, and by Feb. 29, the white, edematous, tender areas, accompanied by erythema and the characteristic reticulated, moth-eaten appearance, were

From the Department of Dermatology and Syphilology, The State University of Iowa.

very marked (Fig. 2.). At that time the experiment was discontinued because of the severe discomfort, all-cotton hose being worn exclusively thenceforth. The affection became somewhat more manifest objectively during the next week, although there was great subjective improvement within 48 hours. After about three weeks the white areas had disappeared. During the following winter the no-nylon regime and the wearing of lightweight, perforated shoes had been continued with rather minimal tendency to the manifestations of vascular disturbance.

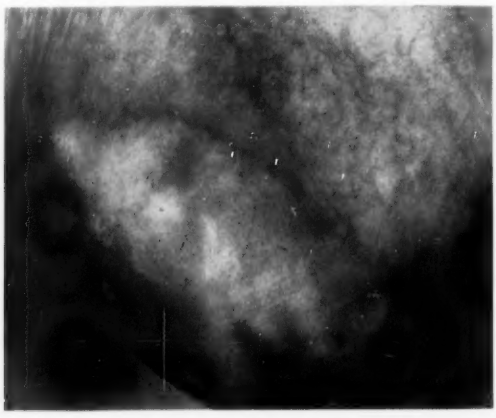

Fig. 1.—Typical edematous, white patches, and the reticulated, moth-eaten appearance of the heel.

Fig. 2.—Left heel shows erythema (darker areas), white, edematous patches, and reticulated skin. Right heel normal.

In retrospect, it is impossible to tell whether any nylon was worn during the first two winters when the condition began. Cotton and silk were worn during the next four years during and after military service.

One additional finding has been constant in the several patients observed with this pernio-like disorder of the feet: Where the tender white patches lie against the canvas or leather lining of the shoe about and beneath the heel, the lining dis-

integrates rapidly (Fig. 3). A glance at the patient's shoes will yield a diagnosis before he has his socks off.

Three additional patients with similar disturbance of the feet have since experienced good relief from the avoidance of nylon footwear.

COMMENT

In this case there appears to be adequate proof that nylon itself can be a contributory factor in at least one dermatosis. The production of the recurrence unilaterally proves the role of nylon. Although there had been a tendency to vascular instability prior to 1948, these attacks were sporadic and responded quickly to foam rubber heel pads. It is possible that some nylon was worn in relation to the early attacks, but this cannot be proved, and there is no intent here to set up nylon as the sole cause of the disturbance. Hosiery containing part or all nylon thread had been

Fig. 3.—Typical disintegration of the shoes associated with this disturbance of the feet, in this case after two months' wear.

worn from 1948 to 1951, during which time the condition recurred, and the use of all-cotton hosiery since that time has greatly alleviated the difficulty.

It does not seem possible that this reaction represents an allergic phenomenon, since there was no reaction other than at the heel even when all-nylon socks were worn. No irritation appeared on the toes, dorsum, or sides of the foot, although these sites are commonly involved in allergies to footwear. It seems likely that the mode of action is through the lack of absorbency of the nylon fabric.

SUMMARY

The wearing of nylon hosiery, or hosiery with nylon reinforcement in the toes and heels, may precipitate or contribute to a pernio-like vasospastic disease of the feet, characterized by redness, swelling, hyperidrosis, and the development of tender, burning, white, edematous patches on and about the soles. This appears to be due to the lack of absorbency of nylon and suggests the possibility that nylon fabrics may promote or contribute to other disorders in which sweating and moisture are factors.

BIBLIOGRAPHY

Anderson, C. R.: Dermatitis from Nylon Hair Nets, Arch. Dermat. & Syph. **61**:111 (Jan.) 1950.

Barton, R. L.: Contact Dermatitis Due to Nylon Hair Net, J. Iowa M. Soc. **40**:224 (May) 1950.

Dobkevitch, S., and Baer, R. L.: Eczematous Cross-Hypersensitivity to Azodyes in Nylon and to Paraphenylenediamine, J. Invest. Dermat. **9**:203 (Oct.) 1947.

Fanburg, S. J.: Dermatitis Following the Wearing of Nylon Stockings: Preliminary Report of 4 Cases, J. A. M. A. **115**:354 (Aug. 3) 1940.

Fleming, A. J.: The Provocative Test for Assaying the Dermatitis Hazards of Dyes and Finishes Used on Nylon, J. Invest. Dermat. **10**:281 (April) 1948.

Jennes, S. W.: Non-Sensitization of Nylon Thread, Indust. Med. **20**:272, 1951.

Schwartz, L., and others: An Outbreak of Dermatitis from New Resin Fabric Finishes, J. A. M. A. **115**:906 (Sept. 14) 1940.

Schwartz, L., and Peck, S. M.: Dermatitis from Wearing Apparel, J. A. M. A. **128**:1209 (Aug. 25) 1945.

EFFECT OF TOPICAL AGENTS ON PLANTAR SWEATING

WALTER B. SHELLEY, M.D., Ph.D.
JOHN J. LASKAS, M.D.
AND
ABRAHAM SATANOVE, M.D.
PHILADELPHIA

THE SWEAT gland of the sole is uniquely protected from external forces. A relatively immense keratinous barrier cushions physical and chemical trauma, and the absence of the pilosebaceous apparatus insures minimal absorption of

Starch paper-iodine foot imprint sweat patterns. Plantar sweating pattern on the right shows normal sweating response in subject's control foot treated for two weeks with talc. Each black dot represents a sweat droplet. On the left is seen the results of two weeks' treatment with Formula A powder (aluminum chloride, etc.). Note the reduction in sweating. This was the exceptional finding.

chemicals and drugs. Because of these exceptional anatomic considerations, it is impossible to include the plantar sweat gland in any generalization regarding the

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From the Department of Dermatology (Dr. Donald M. Pillsbury, Director), University of Pennsylvania School of Medicine.

therapeutic effect of topical agents or measures. Relatively little experimental data have appeared in the literature regarding the effects of topical measures and medicaments on the normal sweat gland of the soles in man.[1] Accordingly, the present study was initiated to obtain further information on this point.

METHODS

All the procedures were tested on normal healthy young men. In all the tests on foot powders and soaks, a paired control method of comparison was employed in which the observer did not know which foot had been treated with the test substance or control. In the observations on iontophoresis, either small areas or the entire sole was treated, and the surrounding area or opposite sole served as a control.

In all instances sweating was graded qualitatively, using the starch paper-iodine imprint technique.[2] The soles were dried, painted with a solution of 3% iodine, and 3% potassium iodide in 95% ethyl alcohol. Immediately after the foot had been fanned dry, the subject stood for two minutes with each foot in the center of a sheet of ordinary stationery paper. Prior to treatment, sweat imprints of the soles of the subjects were taken, and those few showing appreciable differences in the two prints were not included in this study. Sweating was assayed on the basis of appreciable differences in the intensity of the sweat response, (Figure).

1. In the studies of the effect of iontophoresis a simple direct current unit was employed. In the first tests, aqueous solution of atropine sulfate (ranging in concentration from 1 : 200 to 1 : 1000 was used on an electrode covering the entire sole. In the second series, a 1 : 100 scopolamine hydrobromide solution was used. A 6 ma. current intensity was applied from 1 to 10 minutes.

2. The following two foot powders were each tested for effect on 50 subjects:

	Parts
A. Aluminum chloride	3
Boric acid	7
Potassium alum	10
Salicylic acid	3
Starch	5
Talc q.s. ad	100
B. Paraformaldehyde	5
Talcum q.s. ad	100

3. For study on the effects of foot "soaks," three groups of 50 men were employed. The subjects stood for 15 minutes on blotters soaked in aqueous solution of the following agents:

A. Potassium permanganate (1 : 5,000)
B. Formalin (37% formaldehyde)
C. Ammonia water (28% NH_3)

One foot remained untreated for control data. Sweat prints were made at 24 hours and 1 week.

RESULTS

1. *The Effect of Iontophoresis of Anticholinergic Drugs.*—In studies on 30 subjects, using atropine sulfate in aqueous solutions, no inhibition of sweating could be seen in 18 hours. In the second group, of 15 subjects, using 1:100 scopolamine hydrobromide solutions, no local effect on sweating could be detected at 18 hours.

2. *Effect of Foot Powders.*—At the end of two weeks, only three members of the group using powder A daily showed a significant reduction in the sweating rate (Figure). In none was sweating entirely abolished. In the group tested with powder B, only four showed significant reduction.

3. *Effect of Foot Soaks.*—Of the foot soaks, potassium permanganate had no effect. However, a single application of formalin caused a significant reduction in sweating in 41 of the 50 at 24 hours; and after one week in 17; after three weeks, 4 still showed definite reduction in the sweat response. Ammonia water decreased the sweating in 2 of the 50 subjects at both 24 hours and one week.

COMMENT

It is interesting to contrast the absence of effect of iontophoresis of scopolamine on the plantar sweat gland with the effects seen following such iontophoresis on the sweat glands of the back. In a previous study [3] similar iontophoretic procedures on the backs of normal subjects led to a significant anhidrotic effect which persisted for two weeks. In the present study the failure to produce effects on the sole for as little as 18 hours indicated the clinical inapplicability of such a procedure.

The current densities used in the present study are small. It is of interest to note that recently Bouman and Lentzer [4] found that iontophoretic currents per se (to the point of tolerance applied to the sole for 30 minutes for from 5 to 7 times, every other day) produced considerable reduction in the plantar sweating of hyperhidrotic subjects. It is our view that such iontophoretic currents produce mild epidermal damage with consequent sweat pore closure and subsequent temporary sweat retention anhidrosis. Experimentally we have achieved this elsewhere on the body by the use of iontophoresis.[5]

The foot powders used are two examples of currently employed agents * in the treatment of hyperhidrosis.[6] Their relative failure to affect normal sweating is of significance, but may not reflect their actual effectiveness against hyperhidrosis of the soles. Our clinical observations on 20 patients with hyperhidrosis would indicate that powder A was effective in reducing sweating in 25% of the group, as opposed to the 6% seen in the above studies on normal men. It may well be that in the hyperhidrotic subject the powder actually acts in an aqueous phase, permitting more intimate effects on the stratum corneum.

A single application of either dilute permanganate or concentrated ammonia solution was without effect on the sweating of the soles of our normal subjects. Of all the agents tested, formaldehyde alone proved to be really active in reducing sweating. The exact mechanism of producing anhidrosis by formaldehyde foot soaks is not known. It may act either on the sweat gland acini or on the stratum corneum. Unfortunately, formaldehyde frequently acts as a sensitizer or as a severe irritant, and so it cannot be freely used clinically, despite its high index of effectiveness.

It appears that no simple topical method is now available for appreciably inhibiting the normal action of the plantar sweat gland.

CONCLUSIONS

1. Iontophoresis of atropine and scopolamine on the normal sole was without significant effect on plantar sweating.

2. The aluminum chloride and paraformaldehyde foot powders tested proved ineffective in reducing normal sweating of the soles.

* Personal communication from F. J. Knoblauch.

3. Although a single application of dilute potassium permanganate solution or concentrated ammonia water was without effect, a single application of formalin did appreciably reduce plantar sweating for more than one week in 17 of 50 normal subjects.

REFERENCES

1. Ichihashi, T.: Effects of Drugs on Sweat Glands by Cataphoresis, and an Effective Method for Suppression of Local Sweating: Observation on the Effect of Diaphoretics and Adiaphoretics, J. Orient. Med. **25**:101, 1936.

2. Randall, W. C.: Quantitation and Regional Distribution of Sweat Glands in Man, J. Clin. Invest. **25**:761, 1946.

3. Shelley, W. B., and Horvath, P. N.: Comparative Study on the Effect of Anticholinergic Compounds on Sweating, J. Invest. Dermat. **16**:267, 1951.

4. Bouman, H. D., and Lentzer, E. M. G.: The Treatment of Hyperidrosis of Hands and Feet with Constant Current, Am. J. Phys. Med. **31**:158, 1952.

5. Shelley, W. B.; Horvath, P. N.; Weidman, F. D., and Pillsbury, D. M.: Experimental Miliaria in Man: I. Production of Sweat Retention Anhidrosis and Vesicles by Means of Iontophoresis. J. Invest. Dermat. **11**:275, 1948.

6. Hopkins, J. G., Hillegas, A. B., Ledin, R. B., Rebell, G. C., and Camp, E.: Treatment of Hyperhidrosis and Symmetric Lividities of the Feet, Arch. Dermat. & Syph. **57**:850, 1948.

MULTICENTRIC RETICULOHISTIOCYTOSIS OF THE SKIN AND SYNOVIA

Reticulohistiocytoma or Ganglioneuroma

ROBERT W. GOLTZ, M.D.
AND
CARL W. LAYMON, M.D.
MINNEAPOLIS

GANGLIONEUROMA is the title which Montgomery and O'Leary used in 1934 to describe a case characterized by multiple cutaneous tumors, composed of a mixture of inflammatory cells and many large, pale-staining cells with vesicular nuclei. The authors demonstrated granules in the cytoplasm of these cells which they interpreted to be Nissl's granules. They felt that the cells were of neural origin, probably ganglionic; hence the name ganglioneuroma. Others who studied this patient or histologic sections, however, including Senear and Caro, Jaffe, Klemperer, and Foot, denied the neural origin of these cells and made a diagnosis of reticulohistiocytic granuloma.

In 1936, Parkes Weber and Freudenthal presented a man, aged 35, whose illness began with pain and stiffness in various joints, followed by swelling of the knee joints and tendon sheaths on the backs of the wrists. Later he developed pea-sized cutaneous nodules on the backs of the fingers and thumbs and over the ulnar ridges, and a cherry-sized tumor over the right olecranon. Smaller lesions were seen on the ears, face, and buttocks, and over the coccyx. There was a conglomerate, nodular plaque over the back of both acromial regions. There was hypercholesteremia (350 mg. per 100 cc). On histologic examination, there were masses of large cells, mostly multinucleated, with abundant cytoplasm, which contained small amounts of lipid material but was definitely not foamy. When the patient was seen again five years later, there was almost complete regression of the cutaneous lesions but the involvement of the joints had progressed to the point of being disabling.

In 1944, Portugal, Fialho, and Miliano presented, under the title of "generalized giant cell histiocytomatosis," a remarkable case of a man aged 44, who had literally hundreds of cutaneous lesions scattered over almost the entire body. His illness began with arthritic symptoms. Later, punctate and papular tumors appeared on the fingers and hands, ears, trochanteric regions, knees, and forearms. Finally, nodules were found all over the body, except the knees and the feet. The lesions varied in size, were roughly symmetrical, and were most numerous over the bony prominences. Most of them were intracutaneous, but some were fixed to tendon sheaths beneath the skin. Diffuse hyperpigmented infiltrations were seen over the sacrum and buttocks. Later some of the tumors disappeared spontaneously. In addition to the

From the Division of Dermatology, University of Minnesota, H. E. Michelson, M.D., Director; and the Department of Dermatology, Minneapolis General Hospital, Carl W. Laymon, M.D., Director.

cutaneous lesions, there was joint pain and marked limitation of motion of the finger and shoulder joints. Histologically, these nodules consisted of giant cells, and, to a less extent, fusiform cells. An increase in the number of reticulum fibers was demonstrated, and the giant cells were shown to be capable of ingesting injected cholesterol. The authors concluded that the case represented a variety of histiocytoma, but they pointed out the close relationship to synovial lesions.

In 1948, Allen reported two reticulohistiocytomas in which Nissl's granules were not demonstrable in the large cells.

In 1949, Allington presented a patient with lesions on the hands, forearms, and elbows, and the sides of the nose, histologically showing large, acidophilic, granular cells with vesicular nuclei. The diagnoses of ganglioneuroma, histiocytoma, and myoblastoma were considered; subsequently, Allington * concluded that it was an example of reticulohistiocytoma.

In 1950, Zak reported four cases under the heading of reticulohistiocytoma. All had solitary tumors, three arising spontaneously on the face, and the fourth appearing on the leg after trauma. He demonstrated phagocytosis by the large cells and a close association to a reticulum framework.

In 1952, Caro and Senear presented two more examples of this entity. These authors proved the histiocytic nature of the large cells by supravital staining with iron oxide, and preferred the term reticuloendothelial granuloma to reticulohistiocytoma, to emphasize the granulomatous rather than the neoplastic nature of the process.

In discussing Caro and Senear's paper, Montgomery added two more cases which he had studied. The first, a patient of Dr. Bedford Shelmire, had about 150 small, pinhead to pea-sized, reddish tumors scattered on the arms, face, and trunk. The lesions later underwent complete involution. The second patient had an eruption of the scalp, forehead, nose, neck, and arms. She later showed progressive deterioration in health, and nodules developed in the lungs. The nature of the pulmonary lesions was not stated.

The first case which may belong to this group was a patient reported by Targett in 1897. His patient, a woman aged 65, "of rheumatic and gouty habit, and corpulent," had multiple small tumors on the dorsa and sides of the fingers at the base of the ungual phalanges. Microscopically, the tumors consisted of cells with small oval or elongated nuclei in a dense fibrillated ground substance. The striking feature was the large number of irregular, polynucleated, giant cells scattered through the section.

We have had opportunity to study three patients with this entity. One of these was the patient of Dr. Fred Becker, of Duluth, who was described by Caro and Senear. Following is some additional information on this patient, and the report of the two other cases:

Case 1.—E. S., a married woman, aged 40, of American Indian extraction, was first seen at the outpatient clinic of the University of Minnesota Hospitals on Oct. 26, 1950. Her presenting complaints were pain, swelling, stiffness, and limitation of motion in the joints for the previous six months. Her illness began with "flu" in February of 1950, followed by severe sore throat. In April, 1950, she developed pain and stiffness in the neck, followed by similar symptoms in the joints of the extremities. This caused difficulty in walking. She had been treated with salicylates for the previous three weeks.

* In discussion on Caro and Senear.

The thyroid gland had been palpable since childhood, and there had been nervousness, heat intolerance, and moderate dysphagia for the past several years. She had had close contact with her father and a sister while they had active tuberculosis. During her first pregnancy she had had a convulsion, but three subsequent pregnancies had been uneventful. Her weight had dropped from 175 to 146 lb. (79 to 66 kg.) in the past year.

Examination at that time was not remarkable except for the changes in the joints and skin. The joints were red and swollen, and there was definite limitation of motion in the shoulders, elbows, wrists, fingers, knees, and ankles.

Examination of the skin showed 30 to 40 small, smooth papules, up to 3 mm. in diameter, on the forehead and hairy scalp, nape, and scattered over the shoulders and chest. Numerous papules were seen along the sides of the fingers. The lesions were firm, and usually the color of the surrounding skin, but several on the chest appeared purpuric or angiomatous.

The basal metabolic rate was + 10% and a roentgenogram of the chest showed no abnormalties. The sedimentation rate was 40 mm. per hour. The hemoglobin and white cell count were normal.

The patient was admitted to the University Hospitals, service of Dr. C. J. Watson, on April 30, 1952. She then complained of extreme weight loss, weakness, and increasing difficulty in swallowing and breathing. For the past year she had suffered regurgitation of swallowed food without nausea or vomiting. Swallowing was followed by severe discomfort in the chest. The consequent decrease in food intake had caused her to lose 55 lb. (30 kg.) of weight since last seen, in 1950, and her present weight was 87 lb. (39.5 kg.). She had also had dyspnea during periods of excitement. She had an attack of "mumps" in December of 1950, followed by decreased salivation.

On admission the temperature was normal, pulse rate 100, and blood pressure 130/94. There were moderate emaciation and a protuberant abdomen. There were arthritic deformities of the fingers and flexion contractures of the knees. The skin showed the same nodules as had been seen before, but they were notably decreased in number, especially on the face and scalp. A large lymph node was palpable in the right axilla.

The urine and hemogram were normal. Sedimentation rate was 33 mm. in 60 minutes, fasting blood sugar 83 mg. per 100 cc., total serum proteins 8.1 gm. with 3.3 gm. of albumin and 4.8 gm. of globulin. Tests showed normal liver function in view of the elevation of the serum globulin and the state of inanition. Bleeding, clotting, and prothrombin times and serologic tests for syphilis were normal. The Mantoux test was strongly positive in 1 : 1,000 dilution of old tuberculin, U. S. P.

A roentgenogram of the chest showed no evidence of tuberculosis. Roentgenologic studies of the upper gastrointestinal tract showed normal swallowing function with a normal esophagus, stomach, and small intestine. There was no evidence of hiatus hernia. In both femoral necks were cyst-like areas of osteoporosis.

As previously, the basal metabolic rate was + 10%. The I^{131} uptake was 11.5% in 24 hours, which is within the normal range.

Biopsy of the liver showed normal hepatic parenchyma. The enlarged right axillary node showed a granuloma with epithelioid cells, giant cells, and caseation necrosis, and an occasional rod-shaped structure resembling tubercle bacilli. Biopsy of the sternal marrow was unsatisfactory in that it could not be determined whether the material aspirated was actually from the marrow cavity. However, in direct smears three clusters of abnormal cells were seen. These cells had hyperchromatic, large, round to oval nuclei with sharply defined nucleoli. There was abundant pale blue cytoplasm. The cells hung together in clumps. They were apparently identical with the large cells seen in the cutaneous nodules and synovia, to be described below. Sections of the aspirated material showed only clotted blood, but clusters of the abnormal cells were seen in the clot. Subsequent iliac biopsy showed normal bone marrow.

The histologic findings in the skin and joints will be described subsequently.

During her stay in the hospital, the patient showed none of her difficulty in swallowing. The impression was that she had cardiospasm. The nature of her arthritis, previously thought to be rheumatoid, is now in doubt because of the histology of the synovia. Because of the tuberculous lymphadenitis she is now under treatment at a state tuberculosis sanitarium. The primary source of the tuberculosis has not been determined.

CASE 2.—H. V. F., a white man, aged 52, was well until the summer of 1951, when he developed symptoms of a tumor in the large bowel. An operation in September, 1951, revealed an adenocarcinoma of the colon, with involvement of the mesenteric lymph nodes. The tumor was resected, but it was impossible to remove all of the lymph nodes.

The patient recovered uneventfully from his operation and felt well until shortly after Jan. 1, 1952, when, after an exposure to cold and dampness, he suddenly developed aching pain in the back, fingers, knees, and shoulders, plus redness, heat, swelling, and limitation of motion of the involved joints. Simultaneously, multiple small, red, firm nodules appeared at the bases of the fingernails. Within a few days, nodules also developed along the sides of the fingers, and within the next few weeks lesions also were noted on the tops of the fingers, over the knuckles, and on the upper parts of the ears. The lesions were exquisitely tender, so that he was unable to turn a key in a lock because of the pain.

Fig. 1 (Case 2).—Numerous cutaneous nodules overlying and independent of joints of hands. A cluster of small nodules is seen at the base of each nail.

During the period from January until April, 1952, the patient was disabled because of the arthritis, and lost 15 lb. (6.8 kg.) of weight. In the middle of February he developed a cystic swelling, the size of a marble, in the tendon on the dorsum of each wrist.

Examination of Feb. 15, 1952, showed approximately 200 small, red, firm nodules scattered in the skin of the hands and ears. These lesions were oval or circular, varied from 2 to 6 mm. in diameter, and were deeply set in the skin, but apparently not attached to underlying structures. On the hands they were closely studded in the skin at the bases of the fingernails and a group of them was located on the sides of the index fingers. On the dorsal surfaces of the fingers they were most numerous over the distal interphalangeal joints, but they also occurred in smaller numbers in the skin between the joints. On the palmar sides of the fingers, the nodules were less numerous, but a few appeared in the fleshy parts between the joints, particularly in the distal phalanx. A few lesions were seen in the skin of the thenar and hypothenar eminences. Several of the knuckles were overlaid with firm nodules measuring up to 1.5 cm. in diameter.

On the dorsum of each wrist was a walnut-sized cystic mass, apparently attached to the tendon, and becoming smaller on elevation of the arm. These masses appeared to be ordinary ganglia.

The upper half of each ear was similarly studded with small nodules. They were more numerous on the left ear than on the right, and on both ears they were to be found in the largest number along the rim of the ear and on the posterior surface, but also on the anterior surface in smaller numbers.

Several of the nodules were removed for biopsy, and a diagnosis of reticulohistiocytosis was made. On February 28, he was given 40 mg. of long-acting corticotropin (Acthar-Gel). This dose was repeated twice a week for four weeks but there was no apparent effect on the cutaneous lesions and little if any effect on the arthritis. At the same time, fractional doses of superficial x-radiation were given to the involved areas, a total of 575 r being administered to the hands and ears between February and April. The patient noticed that a day or two after each treatment the hands would become bluish and slightly swollen and that the nodules

Fig. 2 (Case 2).—Cutaneous nodules involving almost the entire external ear.

were somewhat less tender but that at the end of the series the lesions were unchanged in size and appearance.

Starting in April, the patient was given a series of injections of Streptococcus vaccine by another physician. He felt that this treatment improved the arthritis. After June, 1952, the cutaneous nodules became less tender, many became smaller, and some disappeared. The disappearance was in roughly the same sequence as their order of appearance.

In the latter part of the summer of 1952, the patient began to lose weight rapidly and to have persistent diarrhea and marked weakness. He developed a large palpable mass in the lower abdomen and a hard, grapefruit-sized mass above the left clavicle. He died in December, 1952. Unfortunately, permission for postmortem examination could not be obtained.

Case 3.—The third patient we have had opportunity to study was Mrs. M. G., the patient of Dr. Fred Becker. This patient was reported by Senear and Caro, but for the sake of completeness we should like to add to her published record the following information:

While under our observation, she stated that she had had pains in the legs ever since she could remember. The pains were at first in the bones, but in 1948 she noted aching in the

knees, followed by swelling and tenderness of both hands, starting in the proximal parts of the finger. Later both wrists became involved. The disability of the hand gradually increased and she noticed the gradual development of flexion deformity in the palms.

At the time of our physical examination (December, 1950), both knee joints were found to contain fluid and were tender. The ankles and elbows were also tender but were not swollen. The fingers were slightly spindle-shaped, and there was a contraction of the palmar tendons bilaterally but no nodules in the tendons. Elevation of the arms at the shoulders was limited to about 80 degrees from the vertical. The cutaneous lesions were as described by Caro and Senear.

Roentgenograms of the hands showed an advanced atrophic arthritis involving the proximal and distal interphalangeal and radiocarpal joints. The skull and long bones were normal. The knee joints showed some loss of normal bone pattern.

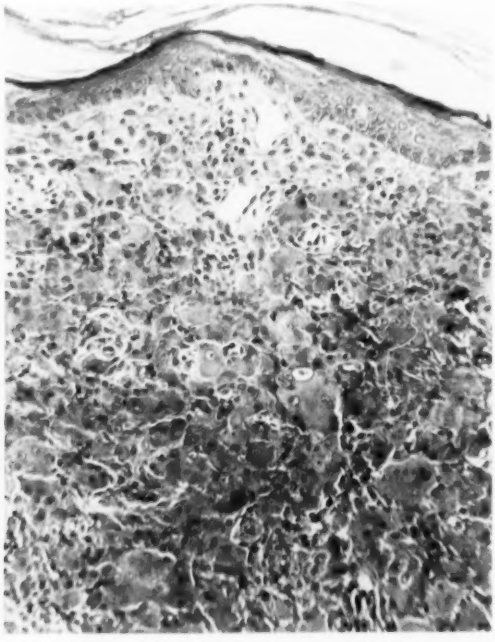


Fig. 3 (Case 2).—Cutaneous lesion. The upper corium is almost entirely filled with histiocytic cells, many of which are giant multinucleated forms. Hematoxylin and eosin stain.

At the time of our examinations the sedimentation rate was 8 mm. per hour, and blood studies were normal. The blood cholesterol was 190 mg. per 100 cc. with 63% esters. The basal metabolic rate was + 10% in December, 1950, and — 4% in March, 1951.

She was again seen by us in February, 1953. At that time the cutaneous lesions had become smaller and less numerous, but many were still present. A synovial biopsy was done, and showed the changes to be described subsequently.

MICROSCOPIC OBSERVATIONS

The following description holds for multiple biopsies taken from all of the three patients that we have studied. The findings in all three patients were practically identical, and there was more variation in different specimens from the same patient than from one patient to another.

Significant changes were limited to the corium. The epidermis was thinned and flattened by the underlying accumulation of cells, but this appeared to be only a secondary phenomenon. In the corium were masses of polymorphic cells. In some sections the cells were to be seen only around blood vessels, in some they were more numerous and occupied an extensive area of the papillary portion, and in others the mass of cells extended throughout almost the entire width of the skin. The cells lay freely in the connective tissue, there being no evidence of encapsulation in any sections.

The cells composing the infiltrate were chiefly histiocytes, with large, irregular, pale-staining nuclei. Scattered among these, however, were a number of cells several times the size of the histiocytes. These giant cells had a large amount of pale-bluish, slightly granular cytoplasm, and from 1 to 20 nuclei, which were usually irregularly

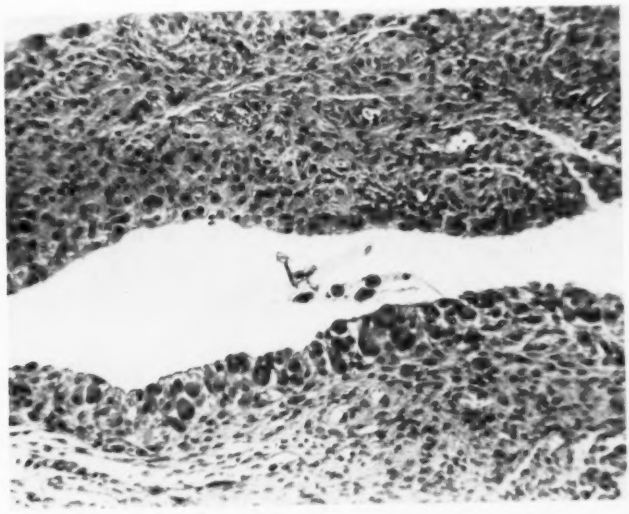


Fig. 4 (Case 1).—Synovial membrane of knee. A layer of giant histiocytes lines the synovial space. In the upper left the same cells are seen deeper in the thickened synovial membrane. Hematoxylin and eosin stain.

arranged in all parts of the cells but in a few cells lay in a semilunar pattern at one pole of the cell. The nuclei had prominent large, deeply staining nucleoli and definite nuclear membranes. The number of giant cells varied widely from section to section. In some they were comparatively few in number, while in others these cells were packed solidly and made up a large part of the cellular infiltrate. Lymphocytes were also present in most of the sections, but they were few in number and not nearly as prominent as they were in some of the previously reported cases. In some sections there were many plasma cells. In most, capillaries in the involved areas were widely dilated and in some instances there was evidence of new capillary formation. Some of the histiocytes appeared to be arising from capillary endothelium. At times there were red blood cells free in the tissue at the periphery of the cellular mass.

With the Van Gieson stain, the collagen fibers were seen to be unaffected except where replaced by the cellular infiltrate. The elastic fibers appeared to be pushed

aside by the masses of cells, surviving only as thickened and clumped fibers between the islands of infiltrate. Stains for reticulum showed the fibers to be more numerous in the areas of the corium which contained infiltrate than in uninvolved areas. In some instances the multinucleated cells were surrounded by a framework of reticulum fibers which lay in close apposition to the cell membrane, but most of the reticulum fibers lay between the multinucleated cells with no close relationship to them.

Stains for hemosiderin were negative in most sections. However, in at least one specimen from the skin, and in the synovial tissue, minute blue granules were to be seen at the periphery of some of the multinucleated cells. It could not be determined whether these granules lay just inside or just outside the cell membrane. Neither thionine nor toluidine blue stains showed any granules which could be interpreted

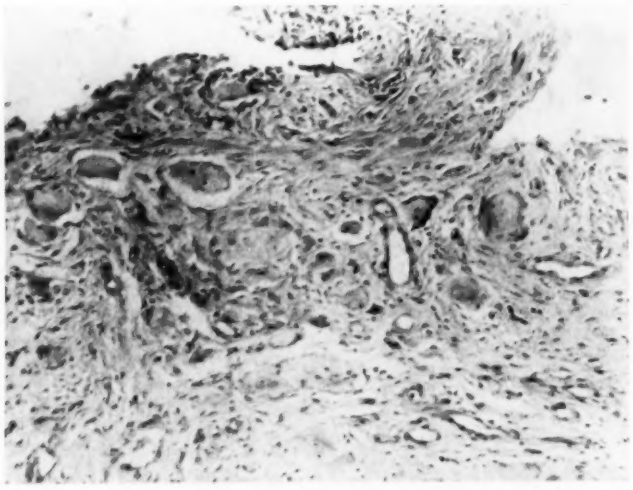


Fig. 5 (Case 3).—Synovial membrane. Toluidine blue stain. No granules are seen in the cytoplasm of the multinucleated cells.

to be Nissl's granules. Acid-fast stains showed no tubercle bacilli in any of the sections of the skin or synovia.

Biopsy of the synovial membrane of a knee joint in Case 1 (E. S.) showed a loose connective tissue stroma which in some places was highly vascular. At the free edges of the membrane, adjacent to the joint cavity, was a layer of histiocytic cells having a large amount of palely eosinophilic cytoplasm. Interspersed among these was a considerable number of giant, multinucleated cells, having the same appearance as those seen in the sections from the skin. The cytoplasm was faintly granular, and the nuclei, numbering up to a dozen in number, had the same prominent nucleoli as seen in those in the skin. In most places the layer was about 20 cells in thickness, but in some areas was many times thicker and formed villous projections into the joint cavity.

By far the greatest number of the cells was found at the free border extending into the synovial cavity, but in at least one area there was a diffuse accumulation

of the giant histiocytes deep in the connective tissue stroma. As mentioned previously, considerable iron was seen to be associated with these cells, in the form of small granules.

The synovial biopsy from patient M. G. showed essentially the same changes.

COMMENT

Fifteen cases probably belonging to this group have now been reported under various titles. In addition, the case reported by Targett in 1897 may be included. Montgomery and O'Leary's case, which they still believe was one of ganglioneuroma, was considered to be one of reticulohistiocytoma by several competent pathologists, and so will be included here for purposes of discussion. These 17 cases can be divided clinically into two main groups: (1) those cases in which there is a striking similarity in regard to the multiplicity and distribution of the cutaneous lesions and

TABLE 1.—*Doubtful, Incompletely Described, and Atypical Cases*

Date	Author	Age of Patient	Sex	Skin Lesions	Remarks
1898	Targett	65	F	Multiple small tumors on backs and sides of fingers at base of ungual phalanges	"Of rheumatic and gouty habit, and corpulent"
1934	Montgomery and O'Leary	..	M	Generalized distribution of lesions	Other pathologists believed the tumors to be reticulohistiocytic granulomas, but the authors favor a neural origin
1948	Allen	..	..	2 patients; no clinical data supplied	One had multiple lesions in the skin (Zak)
1950	Zak				
	Case 1	Adult	M	All solitary tumors	.....
	Case 2	32	M		
	Case 3	45	M		
	Case 4	20	M		
1952	Montgomery (Case of Shelmire)	30	M	Mulitple small tumors on face, arms, and trunk, totaling about 150	Lesions involuted completely; no information about joints or thyroid

the concomitant presence of joint changes or thyroid disturbance, or both, and (2) a group representing those cases in which the clinical picture was atypical or was incompletely described.

The nine atypical or incompletely described cases are summarized in Table 1. Targett's case is chiefly of historical interest. Montgomery still believes the case which he and O'Leary reported in 1934 under the title of ganglioneuroma to be different from reticulohistiocytosis, and the lesions, though numerous and widely distributed, had a considerably different distribution from that common to the eight cases listed in Table 2. Allen gave no clinical data about his two cases. Zak's four cases were unusual in that all had solitary lesions. Shelmire's patient had numerous lesions on the face, arms, and trunk, but no study was made of the joints or thyroid gland.

The remaining eight cases, three of which we have had opportunity to study, are summarized in Table 2. They show some striking similarities. The repeated occurrence of lesions on the sides and dorsa of the fingers, the palms, backs of the hands, sometimes the forearms and elbows, the scalp, forehead, neck, ears, and nose and

nasal septum is noteworthy. This general distribution, with only minor variations, was present in all eight cases. In four of the cases lesions which were diagnosed as ganglia were present on the wrists.

In all eight cases there was either clinical or roentgenologic evidence of arthritis. In seven of the eight the arthritis was moderate to severe, resulting in pain, hot, red and swollen joints, limitation of motion, bony deformity, and, in some cases, synovial

TABLE 2.—*Summary of Eight Reported Cases*

Date	Authors	Age of Patient	Sex	Distribution of Skin Lesions	Arthritis	Thyroid Disease
1936	F. Parkes Weber and Freudenthal	35	M	Fingers, hands, elbows, ears, face, buttocks, over coccyx, acromial regions	Severe arthritis knees, hips, fingers, shoulders; sister had severe rheumatoid disease	Blood cholesterol 350 mg. per 100 cc.
1944	Portugal, Fialho, and Miliano	44	M	Almost generalized, symmetrical, most numerous over bony prominences; first appeared on fingers	Onset with arthritis. Later severe pain, limitation of motion of finger and shoulder joints	Not studied
1949	Allington	68	F	Hands, forearms, elbows, sides of nose; a few lesions over lateral malleoli of ankles; ganglion-like swellings on backs of hands and wrists	Severe arthritis, especially in small joints of hands, wrists and shoulders	Toxic adenoma, BMR +60%, weight loss, nervousness; skin lesions began to involute 3 months after thyroidectomy, as did arthritis
1951	Caro and Senear, Case 1	50	M	Elbows, hands, ears, scalp, forehead, nose, nasal septum, and nape; dorsal surfaces of fingers, palms, and dorsum overlying and independent of joints. Ganglia on wrists	Generalized joint pain and stiffness, diagnosed as rheumatoid arthritis; x-ray of joints showed severe arthritis	Blood cholesterol esters 145 mg. per 100 cc.
1951	Caro and Senear, Case 2, studied by Becker and us	36	F	Face, ears, forearms, V-neck, sides of fingers	Knees, joints of hands, wrists, ankles, shoulders, elbows; contraction of palmar tendons with flexion deformity of hands; x-ray showed advanced and severe atrophic rheumatoid arthritis; synovial biopsy positive	History of goiter and increased nervousness, for which she had taken iodides; BMR and cholesterol normal
1951	Montgomery	24	F	Scalp, forehead, nose, neck, and arms	Swelling of joints, including fingers; effusion in knee joints	.....
....	Our Case 1	40	F	Forehead, scalp, nape, shoulders, upper chest, sides of fingers	Pain, swelling, stiffness and limitation of motion in joints, deformities of fingers, flexion contractures of knees; synovial biopsy positive	Palpable thyroid, nervousness, heat intolerance for many years; great loss of weight, BMR, cholesterol, radioactive iodine uptake normal
....	Our Case 2	52	M	Base of nails, fingers, thenar and hypothenar eminences, ears; ganglia on wrists	Began simultaneously and course paralleled that of cutaneous nodules, finger joints, knees, shoulders, and spine	None

effusions. Most of these patients were considered to have rheumatoid arthritis, but in one gouty arthritis was considered most likely by the roentgenologist, and osteoarthritis was also mentioned. The most commonly involved joints were those of the hands, but the knees, wrists, elbows, shoulders, spine, and jaw were also affected.

In at least four of the patients, there was a noteworthy parallelism in the course of development of the cutaneous lesions and the arthritis. In Allington's patient the arthritis became more severe and extensive while the skin lesions were growing and multiplying. Later, after thyroidectomy, both the arthritis and the cutaneous

lesions improved. In our patient H. V. F. the arthritis and the cutaneous nodules appeared suddenly and simultaneously; both reached their peak at about the same time. Later, as the arthritis improved, the cutaneous lesions regressed.

This striking parallelism in four cases would not seem likely to be the result of coincidence. The occurrence of arthritis in eight cases having a similar eruption, with lesions showing identical microscopic structure, as well as the finding of the same pathology in a synovial membrane as in the skin, indicates that there is a definite connection between the changes in the skin and joints, and that this combination constitutes a disease entity.

The evidence of a relationship of thyroid disease to the cutaneous and joint lesions is considerably less convincing. It is true that three of these eight patients had goiters with symptoms suggesting hyperthyroidism. Allington's patient had a definite toxic adenoma with a basal metabolic rate of +60%, while the manifestations in the skin and joints improved immediately after thyroidectomy. But the other two patients with a history of goiter were found to have normal thyroid function. Weber and Freudenthal's patient had hypercholesterolemia. Of the four remaining patients, Caro and Senear's first patient had a normal level of blood cholesterol esters, our patient H. V. F. had no symptoms of thyroid dysfunction and the gland was not palpable, and Montgomery and Portugal did not mention the status of the thyroid in their patients. There is no convincing evidence, then, that thyroid dysfunction plays a role in the pathogenesis of this syndrome.

Other than the cutaneous lesions, arthritis, and possibly thyroid disease, there is little else in common among these eight patients. All were adults, the oldest being 64 and the youngest 24. Blood studies, liver function tests, and serologic tests for syphilis were normal in all. The bone marrow was consistently normal, with the possible exception of our first patient. The tuberculin test was positive in the two patients in whom it was reported, but only one of the eight had evidence of active tuberculosis. There was no enlargement of the spleen, liver or lymph nodes, or any other evidence of reticuloendothelial disease or blood dyscrasia. Only one of the patients had cancer.

HISTOGENESIS

Several opinions have been expressed by different pathologists concerning the nature of this pathologic process. Among the diagnoses considered when these cases were studied were ganglioneuroma, granular cell myoblastoma, giant cell sarcoma, histiocytoma, xanthofibroma, xanthoma, sarcoidosis, leprosy, metastatic carcinoma, reticuloendotheliosis, and juxta-articular nodes of Jeanselme and Lutz.

We believe that ganglioneuroma can be ruled out in all but Montgomery and O'Leary's case. A considerable mass of evidence has now been accumulated to indicate the origin of the large cells from reticulum cells or histiocytes rather than from neural elements. The cases of Allen, Zak, and Caro and Senear, as well as our own, showed no Nissl's granules when stained with thionine and toluidine blue. Zak interprets the "dendritic processes" reported by Montgomery and O'Leary, and seen in his own cases, to be due to shrinkage of the cells during fixation and staining. The cells have been shown to contain small particles of fat and iron (cases of Zak, Caro and Senear, Weber and Freudenthal, Portugal, Fialho, and Miliano, and our cases). Zak demonstrated phagocytosis of a polymorphonuclear leucocyte by a large cell, and Portugal, as well as Caro and Senear, obtained positive results with supravital staining. Zak showed a close association of a reticulum framework to the large

cells, as did we. Finally, as Zak pointed out, the presence of a large number of inflammatory cells of a mixed character in conjunction with the large cells, a finding which has been reported in almost all of these cases, points toward a granulomatous rather than a neoplastic origin of the process.

The term histiocytoma is, of course, broad enough to encompass a number of concepts, but among dermatologists, at least, it is usually applied to a reaction, occurring in the form of solitary, or at least only a few, tumors, usually developing after injury to the skin. It is considered to be a variant of subepidermal fibrosis in which the cells have not fully changed into fibroblasts but have maintained some of the properties of histiocytes, including the ability to phagocytize fat, hemosiderin, and vital dyes. Multinucleated cells can occur in these, but they are uncommon and never more than few in number, instead of composing a large part of the whole mass, as they do in this condition we are discussing. We feel that histiocytoma, as the term is usually used by dermatologists, can be ruled out on both clinical and pathologic grounds.

The comparison of this process to giant cell tumors of tendon sheath origin was first suggested by Portugal, and later by Fasal, and concurred in by Allington and Beerman. We agree that it is an apt comparison, but we also agree with Portugal and with Caro that this process, while related to the tendon sheath tumors, is not identical to them. It is now recognized that the equivalent of the tendon sheath lesions also occurs in the synovial membranes of the joints and also in relation to bursae. The cytology of these lesions varies widely, even in the same tumor, but many of them consist in part at least of a proliferation of phagocytic histiocytes and numerous giant, multinucleated cells which may contain hemosiderin or lipid material. The cytology may thus be very similar to that in our cases. Dor, Fleissig, Broders, Mason and Woolston, and more recently Jaffe have all been of the opinion that tendon sheath tumors are not true neoplasms, but are of the nature of inflammatory granulation growths. We believe that the condition which we are discussing is also not a true neoplasm but represents a granulomatous response to some as yet undetermined stimulus. This is indicated by the large number of lesions, their benign course with eventual resolution in some cases, and by the fact that the cells have, in most of the reported cases, been of a mixed character, including eosinophiles and lymphocytes, as well as phagocytic histiocytes.

Clinical evidence from these eight cases also indicates a relationship to tumors of the tendon sheaths and synovial membranes. The fact that nodules thought to be ganglia were present in three of these eight patients has already been mentioned. All eight patients were adults, and it has been shown that tendon sheath tumors are confined almost exclusively to adults. There was frequent swelling of the joints, especially the knee, and effusions into the joints, another common occurrence in synovial lesions. The predilection of the process for the hands is notable in both reticulohistiocytosis and lesions of the tendon sheaths and synovia.

In spite of these similarities between the two processes, there are some differences which indicate that, while related, the diseases are distinct from each other. Histologically, the cutaneous lesions differ from typical tendon sheath or synovial tumors by the much greater relative number of giant cells (some of the cutaneous nodules are composed almost entirely of multinucleated cells, and this has not, to our knowledge, been reported in tendon sheath lesions), and by the lack of fibrosis, synovial clefts, or cholesterol crystals, all of which are commonly found in synovial

and tendon sheath lesions. Clinically, the eight cases grouped together in Table 2 all had multiple lesions, often running into the hundreds in number, while tendon sheath tumors are almost always solitary, or, if multiple, only a few lesions are present at one time. The occurrence in one patient of more than a few tendon sheath tumors has never been reported to our knowledge. A crucial difference is, of course, the fact that in the condition which we are discussing, most of the lesions, while they may or may not overlie joints or tendons, histologically are entirely intracutaneous, and no connection to joint space or tendon sheath can be demonstrated.

Despite these arguments against the identity of the lesions of reticulohistiocytosis and tendon sheath or synovial tumors, it should be mentioned that the dermis, tendon sheaths, and synovial membranes are all composed of basically the same kind of cells, namely, histiocytes and fibroblasts, and so it seems entirely possible that the same kind of granulomatous response can occur in all three locations. Indeed, these cases would seem to support strongly the concept of Franceschini and others, that synovial tissue is of reticulohistiocytic nature.

We think that these lesions can be differentiated from xanthoma and xanthofibroma by the fact that there are no foam cells, the giant cells are not of the Touton type, and fat, though it may be present in the form of minute droplets, is not prominent or even consistently present. Nevertheless, the fact that both xanthomas and the lesions of reticulohistiocytosis simultaneously involve synovial tissue and dermal connective tissue, and that in both processes phagocytic histiocytes appear to play a central role, strongly indicates that xanthomatosis and reticulohistiocytosis may be not too distantly related. In this connection, it is interesting to note that Berger included xanthomas under the subgroup of "synovial histiocytomas" in his classification of synovial tumors.

One final possible relationship should be discussed, namely, the relation to Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma of the bone. By and large, we think that the clinical characteristics of the two conditions are sufficiently different so that there should be no confusion between them, and in our material there are marked differences between the histology of Hand-Schüller-Christian, Letterer-Siwe disease, and reticulohistiocytosis, despite the presence of fat-laden histiocytes and multinucleated giant cells in all conditions. However, Ponseti has reported three cases of Letterer-Siwe disease in which the histology of the cutaneous lesions was similar to that in our cases. In one (Case 7), the histology was indistinguishable from reticulohistiocytosis. It should be noted, however, that while this patient undoubtedly died from Letterer-Siwe disease, the cutaneous lesion was not typical of those seen in Letterer-Siwe disease, in that it consisted of a solitary encapsulated tumor which appeared six months before the appearance of systemic manifestations. Nevertheless, the possibility of a relationship between reticulohistiocytosis and the Hand-Schüller-Christian, Letterer-Siwe, eosinophilic granuloma group cannot be completely dismissed.

NOMENCLATURE

In conclusion, we believe that evidence, including the widespread distribution of the lesions in the skin and synovial membranes, and their simultaneous, fairly rapid appearance and disappearance, as well as the character of the cellular infiltrate in the nodules, indicates that they are not neoplastic, but rather a granulomatous response to some unknown but widely acting stimulus. For this reason, the terms

"reticulohistiocytoma" or "giant cell histiocytoma," implying as they do a neoplastic process, do not seem appropriate. Neither does the term "reticuloendothelial granuloma," for the tumors are composed largely of histiocytes and giant cells of connective tissue origin, and there is no evidence that the reticuloendothelial organs are involved in this disease. We would prefer to use some such term as, "multicentric reticulohistiocytosis of the skin and synovia." We are somewhat disturbed at having to include the prefix "reticulo" in this title, since we do not feel that there is conclusive evidence that reticulum cells or fibers participate in the formation of these tumors, but it is felt that such inclusion is necessary in order to establish the connection between our case and those previously recorded, and in order to differentiate this entity from less bizarre histiocytic reactions in other diseases.

SUMMARY

The literature concerning the entity known as generalized giant cell histiocytosis, reticulohistiocytoma, reticuloendothelial granuloma, or reticulohistiocytic granuloma is reviewed, and two more cases are presented.

The relationship of the cutaneous lesions to arthritis is emphasized, and histiologic examination of a synovial membrane, showing the same changes as in the skin, is reported.

A possible relationship to hyperthyroidism is discussed, and it is concluded that a definite connection seems unlikely.

The histologic differential diagnosis is considered, and the nosologic relations of this syndrome are discussed. It would seem that the disease is related to, but distinct from benign tumors of synovial and tendon sheath origin, and to xanthomatosis, and possibly also to the Hand-Schüller-Christian, Letterer-Siwe, eosinophilic granuloma group of diseases.

The disease is thought to represent a widespread granulomatous response to an unknown stimulus, rather than being truly neoplastic in nature.

In order to describe these relationships, the designation "multicentric reticulohistiocytosis of the skin and synovia" is proposed.

BIBLIOGRAPHY

Allen, A. C.: Survey of Pathologic Studies of Cutaneous Diseases During World War II, Arch. Dermat. & Syph. **57**:19 (Jan.) 1948.

Allington, H. V.: A Case for Diagnosis (Ganglioneuroma? Histiocytoma? Myoblastoma?), Arch. Dermat. & Syph. **62**:452 (Sept.) 1950.

Berger, L.: Synovial Sarcomas in Serous Bursae and Tendon Sheaths, Am. J. Cancer **34**:501 (April) 1938.

Broders, A. C.: Benign Xanthic Extraperiosteal Tumor of the Extremities Containing Foreign-Body Giant Cells, Ann. Surg. **70**:574 (Nov.) 1919.

Caro, M. R., and Senear, F. E.: Reticulohistiocytoma of the Skin, A. M. A. Arch. Dermat. & Syph. **65**:701 (June) 1952.

Dor, L.: Relations de tumeurs à myéloplaxes et des xanthomes, Assoc. franç de chir. **12**:553, 1898.

Fleissig, J.: Über die bisher als Riesenzellensarkome (Myelome) bezeichneten Granulationsgeschwulste der Sehnenscheiden, Deutsch. Ztschr. Chir. **122**:239, 1913.

Franceschini, P.: Ricerche istologische sulle articolazioni, Arch. ital. anat. e embriol. **27**:76 (Sept.) 1929.

Jaffe, H. L.; Lichtenstein, L., and Sutro, C. J.: Pigmented Villonodular Synovitis, Bursitis, and Tenosynovitis, Arch. Path. **31**:731 (June) 1941.

Mason, M. L., and Woolston, W. H.: Isolated Giant Cell Xanthomatic Tumors of the Fingers, Arch. Surg. **15**:499 (Oct.) 1927.

Montgomery, H., and O'Leary, P. A.: Multiple Ganglioneuromas of the Skin, Arch. Dermat. & Syph. **29**:26 (Jan.) 1934.

Ponseti, I.: Bone Lesions in Eosinophilic Granuloma, Hand-Schüller-Christian Disease, and Letterer-Siwe Disease, J. Bone & Joint Surg. **30-A**:811 (Oct.) 1948.

Portugal, H.; Fialho, F., and Miliano, A.: Histiocitomatosis gigantocitaria generalizada, Rev. argent. dermatosif. **28**:121 (June) 1948.

Targett, J. H.: Giant-Celled Tumors of the Integuments, Tr. Path. Soc. London, **48**:230, 1897.

Weber, F. P.: Cutaneous and Subcutaneous Nodules, with Juxtaarticular Infiltrations and Rheumatoid Symptoms, Brit. J. Dermat. **55**:1 (Jan.) 1943.

Weber, F. P.: A Syndrome of Rheumatoid Arthritis Combined with Multiple Xanthomatous Connective-Tissue Infiltrations, in Rare Diseases and Some Debatable Subjects, Ed. 2, London, Staples Press, Ltd., 1947, p. 39.

Weber, F. P., and Freudenthal, W.: Nodular Non-Diabetic Cutaneous Xanthomatosis with Hypercholesterolaemia and Atypical Histological Features, Proc. Roy. Soc. Med. **30**:522, 1937.

Willis, R. A.: Pathology of Tumors, St. Louis, C. V. Mosby Company, 1948, p. 695.

Zak, F. G.: Reticulohistiocytoma ("Ganglioneuroma") of the Skin, Brit. J. Dermat. **62**:351 (Sept.) 1950.

PANTHODERM

A Topical Therapeutic Adjuvant

ASHTON L. WELSH, M.S., M.D.
AND
MITCHELL EDE, M.D.
CINCINNATI

ANIMAL experiments suggest [1] and clinical observations confirm [2] that the topical application of pantothenic acid, a nutritional factor of the vitamin B group, favors regeneration and functional recovery of damaged epithelium in dermatoses of various causes.[3]

Response obtained by one of us with derivatives of pantothenic acid when administered in massive doses orally, in combination with vitamin E, in the treatment of certain phases of lupus erythematosus and in granuloma annulare,[4] stimulated interest in a study of the therapeutic value of Panthoderm* (a water-miscible cream containing 2% pantothenyl alcohol), topically, for lesions of lupus erythematosus. Study was accordingly undertaken of this material as a topical therapeutic adjuvant to the internal regimen mentioned above.

Panthoderm was used, topically, by 26 private-practice patients with lupus erythematosus. Patients are classified according to the disease phase presented:

No. of Patients	Disease Phase
15	Chronic discoid
8	Disseminated discoid
3	Subacute disseminated

The longest period of therapy was 13 months; the average, 8 months.

Of the 15 patients with chronic discoid lesions, 1 patient developed eczematization following use of Panthoderm—such eczematization being confined to the discoid lesions, sparing adjacent normal skin. This reaction was mild, of short duration, and easily controlled. Another patient manifested excessive dryness of the discoid lesions on the scalp, and was placed on other therapy. Thirteen patients showed improvement in the skin lesions, in that erythema subsided, infiltration and follicular plugging lessened, hypertrophy diminished—at an accelerated rate compared to previous progress on the oral massive-dose therapy with derivatives of pantothenic acid and vitamin E alone.

Of the eight patients with disseminated discoid lesions, use of Panthoderm was withdrawn in one patient. In this patient, increased inflammation and extension of existing lesions with development of new lesions were manifestations of exacerbation of the disease due to exposure to sun in a very sun-sensitive person, rather than to a contact reaction to Panthoderm. One patient felt that the cream "was irritating."

* Dr. Louis Freedman of the U. S. Vitamin Corporation supplied the Panthoderm used in this study.

and therapy was stopped, although no evidence of reaction was apparent. Six patients showed accelerated improvement over that obtained with the oral program alone. For two patients, who had oral ulcerated lesions, Panthoderm, applied by massage several times daily, produced amazingly prompt re-formation of mucous epithelium.

Three patients in the subacute disseminated group tolerated the material and showed some expedited cutaneous improvement over that produced by the oral program alone.

Results were observed following use of Panthoderm in 28 patients with the disease entities shown in the Table (for some of which prolonged trials of therapy with other agents had produced indifferent results). This group of patients was not on the internal massive-dose program previously mentioned.

Results in Various Disease Entities

No. Patients	Diagnosis	Duration of Disease, Yr.	Results
3	Hypostatic dermatitis with ulceration	9-14	Excellent; epithelization rapid; growth of granulation tissue accelerated
9	Pruritus ani et vulvae and senile vulvitis	3-10	Good; areas of excoriation and fissures healed; maceration and lichenification markedly improved; pruritus relieved; some evidence of antibacterial activity on vaginal epithelium
4	Atopic dermatitis and neurodermatitis	10-20	Good; infiltration lessened; pruritus controlled
5	Leukoplakia and perleche	1+	Good, particularly in areas of perleche of the malocclusion type
4	Dermatofibroma lenticulare and seborrheic keratoses	Lesions fulgurated	Excellent; marked stimulation of growth of granulation tissue and epithelization in resultant ulcers
2	Psoriasis	5-10	No apparent effect on psoriatic lesions
1	Erythroderma ichthyosiforme congenitum	Life	No improvement, but material was comforting when other materials were not tolerated

Response of three patients in the hypostatic-dermatitis-with-ulceration group was striking for acceleration of formation of granulation tissue. Incorporation of more active bacteriostatic agents gave evidence that Panthoderm may be a vehicle of choice in such conditions. Response of nine patients with anal and vulvar lesions was striking for disappearance of maceration, thinning of lichenified plaques, and control of pruritus. Incorporation of estrogenic substances for several patients, particularly those with senile vulvitis, gave further evidence of the usefulness of Panthoderm as a vehicle.

SUMMARY AND CONCLUSION

Twenty-two (of a group of 26) patients with various phases of lupus erythematosus on massive oral dose therapy of derivatives of pantothenic acid combined with vitamin E manifested some clinical evidence of additional response when Panthoderm was used as a topical therapeutic adjuvant. Response was impressive in two patients with oral ulcerated lesions.

Twenty-five (of a group of 28) patients with disease entities other than lupus erythematosus, not on the internal therapeutic regimen above mentioned, evidenced stimulation of epithelization (most marked in hypostatic dermatitis with ulceration), resolution of maceration, and healing of fissures and of excoriations (in pruritus ani et vulvae and senile vulvitis).

Panthoderm is an effective and well-tolerated vehicle for the transport of other medicaments.

There was no evidence of sensitization.

1219 Carew Tower.

REFERENCES

1. Spies, T. D.; Stanbery, S. R.; Williams, R. J.; Jukes, T. H., and Babcock, S. H.: Pantothenic Acid in Human Nutrition, J. A. M. A. **115**:523 (Aug. 17) 1940.

2. Combes, F. C., and Zuckerman, R.: Panthenol: Its Topical Use in Cutaneous Ulceration, J. Invest. Dermat. **16**:379 (June) 1951.

3. Kline, P. R., and Caldwell, A.: Treatment of Various Dermatoses with Topical Application of Panthenol, New York J. Med. **52**:1141 (May) 1952.

4. Welsh, A. L.: Lupus Erythematosus: Treatment by Combined Use of Massive Amounts of Calcium Pantothenate or Panthenol® with Synthetic Vitamin E, A. M. A. Arch. Dermat. & Syph. **65**:137 (Feb.) 1952; Lupus Erythematosus. Treatment by Combined Use of Massive Amounts of Pantothenic Acid and Vitamin E, ibid., to be published; Granuloma Annulare. Response to Massive Dose Therapy of Vitamin E Combined with Pantothenic Acid Derivatives, ibid., to be published.

SOIL-EXTRACT AGAR FOR CANDIDA ALBICANS

ALEXANDER BAKERSPIGEL, M.A.
EDMONTON, ALTA., CANADA

SPECIES of Candida isolated from patients can be differentiated morphologically when grown on a nutrient-poor medium such as cornmeal agar. I recently described a yellow cornmeal agar medium for such purposes and showed that on it Candida albicans can usually be identified by its chlamydospores in one to three days.[1]

In this laboratory a soil-extract agar is used as an alternative medium to the yellow cornmeal agar. Results obtained in the identification of 424 "yeast" cultures from Alberta patients show this medium to be as satisfactory as the yellow cornmeal medium for the identification of C. albicans and other species of Candida.

MATERIALS AND METHODS

Preparation of Soil-Extract Agar Medium.—Approximately 1 liter of fine, sandy loam[2] is added to 1 liter of distilled water in an enamel pot, and the mixture is autoclaved for 15 minutes at 15 lb. pressure. The supernatant upon cooling is filtered through two changes of coarse filter paper (Reeve Angel 202); 500 ml. of the filtrate is made up to 1,000 ml. with distilled water; 15 gm. of agar is added, and the mixture is autoclaved in a cotton-plugged flask at 15 lb. pressure for 20 minutes. No adjustment of pH is necessary. After cooling to 50 C., the medium is dispensed in 20-ml. amounts in sterile Petri plates.

Comparison of Two Media for Identification of C. Albicans

	Yellow Cornmeal Agar	Soil-Extract Agar
Number identified as C. albicans	244	242
% of total identified	100	99.2

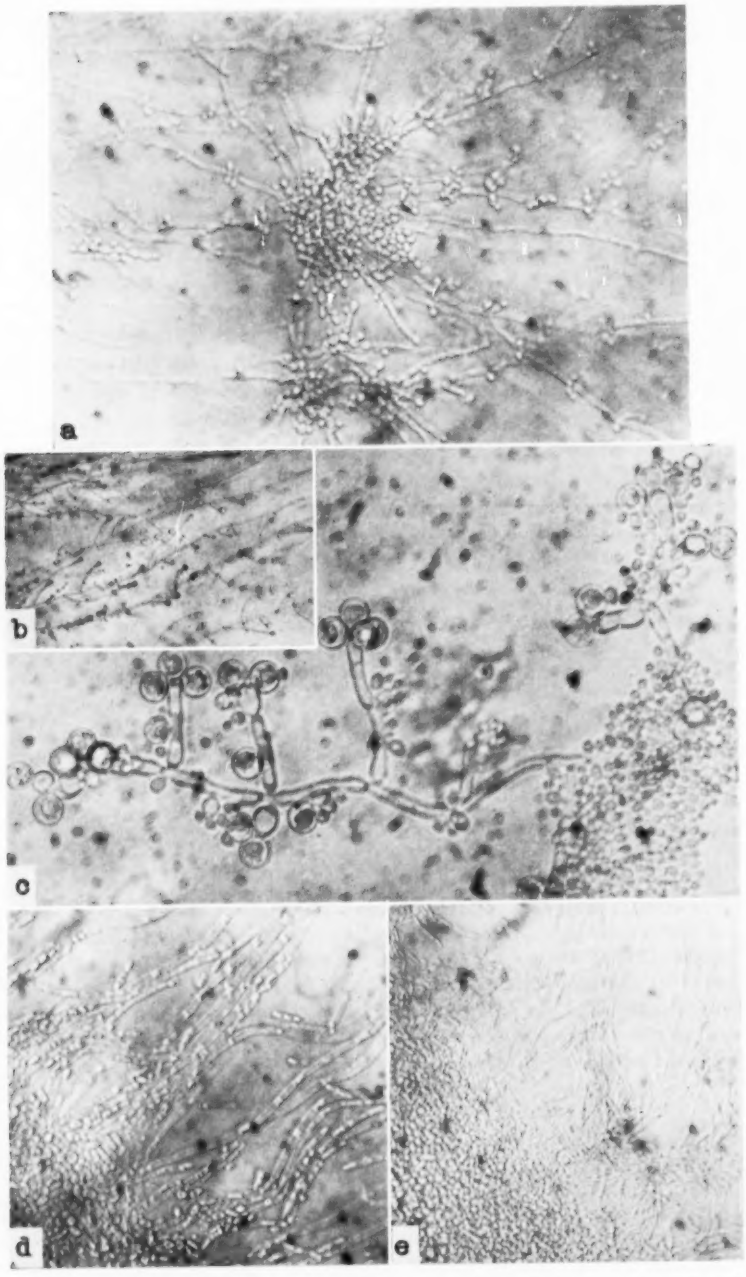
Inoculation of Medium and Identification of Cultures.—The methods used for inoculation and identification of the cultures are the same as those outlined previously by me,[1] by Martin and associates,[3] and Lodder and Kreger-van Rij.[4]

RESULTS

Of the 424 "yeast" cultures examined, 244 were identified as C. albicans, the remaining 180 as C. tropicalis, C. krusei, C. guilliermondi, and various other "yeasts."

The Table shows that soil-extract agar medium is as satisfactory as yellow cornmeal agar for the identification of C. albicans.

From the Provincial Laboratory of Public Health, University of Alberta. This work was made possible by a Provincial Health Grant to Dr. E. S. Dowding.



Species of Candida on soil-extract agar medium. *a*, C. tropicalis; *b* and *c*, C. albicans; *d*, C. Krusei, and *e*, C. guilliermondi. Magnification: *a*, *d*, and *e*, × 200; *b*, × 64; *c*, × 670.

The morphology, arrangement of pseudomycelium, blastospores, and chlamydospores of 3-day-old cultures of Candida ssp. on soil-extract agar are seen in the Figure (*a* to *e*). C. tropicalis has a well-developed, branched pseudomycelium with single or branched verticils and numerous blastospores, some in chains (Fig. *a*). C. albicans forms on this medium an abundance of characteristic thick-walled chlamydospores and clusters of blastospores (Fig. *b* and *c*). C. krusei has a well-developed mycelium with elongate or cylindrical blastospores (Fig. *d*), while C. guilliermondi forms a pseudomycelium made up of stalagmoid cells and round or stalagmoid blastospores (Fig. *e*).

SUMMARY

A soil-extract agar medium is described for the identification of C. albicans and other Candida species.

REFERENCES

1. Bakerspigel, A.: A Preferred Method for the Routine Identification of Candida, J. Infect. Dis., to be published.

2. Bakerspigel, A.: Soil as a Storage Medium for Fungi, Mycologia **45**:596-604, 1953.

3. Martin, D. S.; Jones, C. P.; Yao, K. F., and Lee, L. E.: A Practical Classification of the Monilias, J. Bact. **39**:609-630, 1940.

4. Lodder, J., and Kreger-van Rij, N. J. W.: The Yeasts: A Taxonomic Study, New York, Interscience Publishers, Inc., 1952.

Clinical Notes, New Instruments and Techniques

TREATMENT OF PSORIASIS WITH LARGE DOSES OF VITAMIN B_{12} 1,100 MICROGRAMS PER CUBIC CENTIMETER

Preliminary Clinical Report

RUDOLPH RUEDEMANN Jr., M.D.
ALBANY, N. Y.

Vitamin B complex in various forms has been used as an adjunct in the treatment of both psoriasis and seborrheic dermatitis.[1] About three years ago, again with use of sunlight, crude coal tar (a modified ambulatory Goeckermann routine), with vitamin B_{12} capsules (25 γ), a low-fat, and pork-free diet, improved results were attained, but slowly, with some lack of cooperation on the part of the patient. Vitamin B_{12} injections of 30 γ per cubic centimeter were added at weekly intervals with no phenomenal improvement over previous methods other than improving the well-being of the patient. It was advocated that 20 γ of vitamin B_{12} a week would suffice, although it is rapidly excreted in 24 hours.

In the spring of 1953, vitamin B_{12} of 1,000 γ per cubic centimeter was suggested for neuritis, arthritis, and vascular disorders. This dosage of 1,000 γ per cubic centimeter was incorporated in the routine treatment of psoriasis—first at weekly intervals, but quickly changed to a series of daily intramuscular doses of 1 cc. of 1,000 γ per cubic centimeter. A rapidity of the involution of recalcitrant eruptions beyond expectations was experienced. The vitamin B_{12} prepared from Streptomyces griseus was used. Investigative work must be carried on to ascertain if there is a difference in therapeutic results when vitamin B_{12} from different sources, natural or synthetic, is used. Some investigators maintain there is a difference.

Sixty-three patients have been put under treatment since March, 1953. Thirty-four patients have been under treatment two months or longer; observations are based on these patients. Follow-up entailed some difficulty; 60% of the patients (as they were from out of town) were under the care of their local physician. Injections were not always carried on by the physician as many patients were from small communities.

It was found early in the treatment that 1 cc. of a 1,000 γ dose given intramuscularly daily for 10 days consecutively, followed by a maintenance dose, gave best results, and in severe cases daily doses were carried on for 15 to 20 days or longer, consecutively. In some refractory cases, no results were noted until 20 or more injections were given. Experience will eventually point out the best routine. No reactions, local or general, were encountered, but marked improvement as to well-being, with more zest to carry on, was observed by all the patients.

There were 34 patients—14 male, 20 female—ranging from 21 to 68 years of age. The duration of the disease varied from 7 months to 38 years.

11 patients eruption involuted

10 patients improved 75 to 80%

6 patients slowly improving; treatment continuing

2 patients no results (women)—not cooperative—one weighed 280 lb. (127 kg.), the other 220 lb. (99.8 kg.)

5 patients slight recurrence; treatment stopped too soon; resumed with good results

There were six patients with severe pruritus and three with genitocrural and perianal psoriasis, which is too often misdiagnosed in females. They reported that the pruritus had subsided after two or three treatments.

Associate Professor of Dermatology and Syphilology, Albany Medical College.

SUMMARY

Treatment with high doses of vitamin B_{12}—1,000 γ per cubic centimeter, intramuscularly—has surpassed all previous methods in rapidity of results: lack of reactions, ease of administration, stimulating cooperation, and bolstering the well-being of the patient.

The rapid response (under vitamin B_{12} injections) of patients with long-standing recalcitrant psoriasis would be difficult to attribute to spontaneous involution.

The results are too constant to deny some therapeutic value in vitamin B_{12} injections, and wholesale clinical trials are indicated.

Special diet, tar baths, and sunlight as adjunct treatment (particularly diet) may be indicated for the present.

The present dosage is gauged by the severity of the disease and the response.

Psoriasis tends to recur; time will tell.

Seborrheic dermatitis is under investigation, and indications point to similar response.

Maintenance doses of one or two injections a week is carried on in some patients at present.

REFERENCE

1. Andrew, G. C.; Post, C. F., and Domonkos, A. N.: New York J. Med. **50**:1921 (Nov.) 1949.

MECHANICAL METHOD OF FREEZING THE SKIN FOR SURGICAL PLANING

PAUL LE VAN, M.D.
LOS ANGELES

Since the development of the surgical planing technique, as described by Kurtin,[1] this method of skin abrasion for improvement of acne scars and other cosmetic skin defects has received wide acceptance. Plastic surgeons and dermatologists alike are employing this procedure on a wide scale. As with any new therapeutic modality, improvements in technique and determination of its indications must be accomplished.

Approximately one year ago, when I first utilized the planing technique, it was apparent that the method of applying ethyl chloride to the skin for topical anesthesia was cumbersome, variable in intensity of freezing, and left little time for the actual planing. The technique, as then applied, consisted of the operator's holding a bottle of ethyl chloride in each hand and an assistant's directing a stream of air to the area to be frozen. An alternative method employed the use of a blower mounted on a stand which could be directed to the area. After freezing had occurred, the operator had to place the bottles on a stand and then pick up the handpiece of the planing apparatus. The time involved in this procedure allowed for thawing of the frozen area to begin and progress. In order to obviate these technical defects, a mechanical device was designed which would deliver the ethyl chloride spray under a stream of compressed air to the site to be treated (Fig. 1). The entire procedure is controlled by a foot pedal, leaving the operator's hands free to begin planing as soon as freezing has occurred. The apparatus developed for the purpose is herewith described:

The spraying unit consists of a bracket designed to direct the streams from two ethyl chloride 4 oz. (113 gm.) bottles with lever controls to a point on the skin where an air stream strikes under about 20 lb. pressure per square inch. The evaporation of the ethyl chloride is hastened by the air stream, so that almost instantaneous freezing results. The air stream is obtained from a regular dental-type air compressor or a tank of compressed air. The tube directing the air stream can be extended to point at the spot to be planed and then be retracted to control the size of the

From the Division of Dermatology, Department of Medicine, University of California Medical Center at Los Angeles.

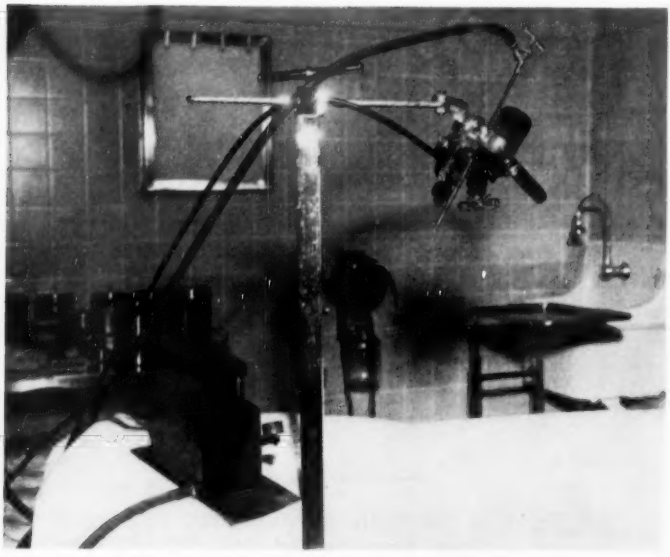


Fig. 1.—Close-up view of ethyl-chloride bracket and foot-pedal control.

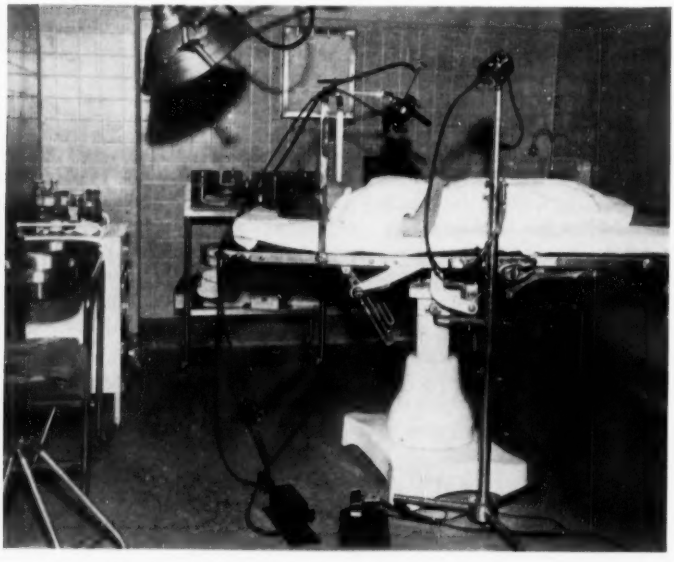


Fig. 2.—Mechanical freezer in position, ready for use.

area of freezing. This tube also has a control valve to regulate the air pressure. The compressed air and ethyl chloride streams are controlled simultaneously by a foot pedal that opens a valve for the air and pulls an automobile choke-type flexible tube and wire control, which presses against levers opening the ethyl chloride bottles. The spray head allows the two streams of freezing material to be converged at any required distance. The spot where the air and ethyl chloride streams converge is determined by preoperative trial.

The device is positioned over the operating area by a ¼ by 1 in. cold-rolled steel bow with side-pieces spaced to fit in the standard sockets on the sides of a treatment table and elevated according to the part to be operated on. The cross piece of the bow carries a clamp movable crosswise and holding another bar moving longitudinally to the table with the spray unit attached with a universal joint at the end. By turning the spray unit end either way and selecting proper brackets on the treatment table, one can direct the spray at any angle to any part of the body, and by using the handle attached to the spray unit, can direct the spray to follow in any direction as the operation proceeds.

It has been found that with use of the above-described topical anesthesia machine, almost instant freezing occurs in the area to be treated. The operator can begin work at once as soon as the tissues become rigid, and, should a more prolonged anesthesia be desired, it can be accomplished by depressing the foot pedal without cessation of the planing procedure. Similarly, the assistant's hands are completely free at all times to execute procedures necessary in the planing operation. It must be borne in mind that too lengthy freezing of the skin may prove injurious. The ease with which the topical anesthesia is delivered by the jet spray may lead to excessive freezing in inexperienced hands. Despite this potential danger, it has been found in a series of 110 planings that the jet spray automatic topical freezer contributes much to the ease, efficiency, and speed of surgical planing of the skin.

REFERENCE

1. Kurtin, A.: Corrective Surgical Planing of Skin, A. M. A. Arch. Dermat. & Syph. **58**:389-397 (Oct.) 1953.

DERMATITIS MEDICAMENTOSA

A Lichen-Planus-like Eruption Due to Quinidine

HARRY L. WECHSLER, M.D.
McKEESPORT, PA.

A variety of adverse reactions to quinidine have been reported since Frey [1] in 1918 found the drug to be more effective in cardiac arrythmias than its levorotary isomer quinine. These reactions are of two types, acquired sensitivity and drug toxicity.[2]

Manifestations of acquired sensitivity are thrombocytopenic purpura,* fever,† and skin eruptions. The toxic reactions are characterized by cinchonism, the commonest adverse reaction; cardiac standstill or ventricular tachycardia; syncope; convulsions, and respiratory difficulties.‡ Most patients with acquired sensitivity also experienced manifestations of cinchonism.

Goldschlag [15] in 1942 reported the occurrence of a symmetrical eczematoid dermatitis from quinidine. After his patient had taken the drug for a period of two months, a scaling, pruritic, edematous eruption appeared on the exposed areas of the skin. On two occasions the eruption

From the Department of Dermatology, College of Physicians and Surgeons, Columbia University and The Vanderbilt Clinic, Presbyterian Hospital, New York.

* References 3 to 7.

† References 8 to 11.

‡ References 12 to 14.

disappeared promptly after quinidine was discontinued. However, when quinidine was given again, the eruption recurred as a severe pruritic, violaceous-colored, exudative dermatitis. This was accompanied by an erythema of the trunk and purpura of the legs.

Taylor and Potashnick [13] in 1951 described a patient who developed a pustular eruption on the hands and feet while taking quinidine. Although this dermatitis cleared when penicillin was given, a diffuse maculopapular eruption which subsequently developed went on to generalized exfoliation. The exfoliation subsided when quinidine was discontinued but returned when the drug was reinstituted.

The following case report is that of a lichen-planus-like eruption due to quinidine.

M. B., a 56-year-old white married woman with controlled diabetes and asymptomatic arteriosclerotic heart disease, experienced sudden onset of paroxysmal auricular tachycardia in February, 1953. Since there was no untoward reaction to a test dose, quinidine sulfate was given, 0.4 gm. three times daily. Five days later, because of the onset of dizziness, an unstable gait, tinnitus of the left ear, and hyperhidrosis, the dosage was reduced to 0.2 gm. three times daily. Although the dizziness and ataxia subsided, the other symptoms persisted.

The patient was referred to the dermatology clinic in June, 1953, because of a dermatitis of two weeks' duration. The patient stated that after she had taken quinidine for three months a pruritic eruption appeared on the dorsa of the hands. This soon spread to involve the forearms, legs, and neck. The eruption seemed to be intensified by exposure to sunlight.

Examination revealed a dark-complexioned white woman with a pruritic, diffuse, papular eruption involving the extensor surface of the hands, arms, legs, and sides of the neck. The papules were 3 to 5 mm. in diameter, regular in outline, flat-topped, and violaceous in color; some tended to coalesce and form nummular patches. A grayish-white cobweb-like network was noted in some of the lesions. On the neck the papules appeared to follow the lines of cleavage.

The impression was that the patient had a lichen-planus-like drug eruption probably due to quinidine. However, she was permitted to continue on the drug. One week later the eruption had become more intense and involved the lower lip and the buccal mucosa. The lip was edematous and exhibited an erythematous, furfuraceous scaling eruption. The buccal mucosa contained slightly elevated whitish patches.

A biopsy specimen was taken from the right side of the neck. Sections of the tissue, stained with hematoxylin and eosin, were read by Dr. Gerald F. Machacek. Microscopic examination revealed a hyperkeratotic epidermis, which varied in width and showed some spongiosis. An absolute hyperkeratosis was present over areas of hypergranulosis and acanthosis. The basal layer showed liquefaction degeneration. The epithelium of the hair follicles was similarly involved, and the infundibula contained compact keratin plugs. In the subepidermal cutis was a narrow zone of lymphocytic infiltration. The histologic picture was characteristic of lichen planus. However, a finding not usually seen in lichen planus was a microscopic hemorrhage in some areas of the papillary cutis.

Quinidine was discontinued. Within three days the pruritus and photosensitivity subsided, and the eruption was fading. Five days after quinidine was discontinued only a few faintly pigmented macular lesions on the neck remained.

One evening three weeks later, the patient experienced onset of palpitations. She took 0.1 gm. of quinidine. In six hours there was pruritus and erythema at the previously involved sites. The next morning after being in the sunlight, the patient noticed the recurrence of the lichen-planus-like lesions within a few hours. No more of the drug was taken, and the eruption disappeared in three days.

While the patient was taking quinidine, an attempt was made to evaluate the sensitivity to sunlight. This was done by exposing 2.5 sq. cm. areas on the patient's back to the Kromayer ultraviolet light. Five seconds' exposure produced erythema and pruritus within 30 minutes; pigmentation was present within 48 hours. The patient was retested to the Kromayer ultraviolet light six weeks after she had discontinued the drug. There was neither pruritus nor erythema after 15 seconds' exposure. Slight pigmentation was present within 72 hours.

COMMENT

The repeated occurrence of the lichen-planus-like eruption while quinidine was being taken and the prompt disappearance of the eruption upon discontinuance of the drug leave little doubt that quinidine may produce a lichen-planus-like drug eruption. Arsenic, arsphenamine, gold, thallium, quinacrine (Atabrine), and paraaminosalicylic acid produce lichen-planus-like eruptions, but there was no history of taking such drugs in this case.

This eruption is different from the eczematous dermatitis reported by Goldschlag and the exfoliative dermatitis reported by Taylor and Potashnick. However, drugs that are known to give rise to lichen-planus-like eruptions may also cause an eczematous and exfoliative dermatitis.

Acquired sensitivity to quinidine is apparent in this patient by the initial prolonged exposure period and by the reproduction of the eruption after a markedly shortened exposure when a very small amount of the drug was taken. These findings are consistent with those noted in thrombocytopenic purpura and fever—the most frequently reported sensitivity reactions to quinidine. Symptoms of cinchonism preceded the onset of the eruption in this patient, as has been pointed out for most of the patients with acquired sensitivity. This may well be a warning sign of developing sensitivity.

Although the mechanism of this allergic cutaneous reaction to quinidine is unknown, photosensitivity appears to be a factor. This is attested to by the occurrence of the lesions on the exposed areas of the skin, the increased sensitivity to ultraviolet light while the patient was receiving the drug, and the loss of this sensitivity after discontinuance of the drug. Sunlight hastened the recurrence of the characteristic lesions after the last dose of quinidine. Photosensitivity seemed to accentuate and localize the eruption rather than produce it.

SUMMARY

In the treatment of cardiac arrythmias with quinidine adverse reactions may occur. These reactions may be of the acquired sensitivity type and of the toxic type.

A case is reported in which cinchonism preceded an allergic drug eruption indistinguishable from lichen planus.

The photodynamic action of quinidine may have accounted for the accentuation and location of the lesions.

324 Shaw Ave.

REFERENCES

1. Frey, W.: Weitere Erfahrungen mit Chinidin bei absoluter Herzunregelmässigkeit, Klin. Wchnschr. **55**:849-853, 1918.

2. Stimson, W. H., and McKusick, V. A.: Febrile Reactions to Quinidine, Am. J. Med. Sc. **221**:440-443 (April) 1950.

3. Broch, O. J.: Thrombopenisk purpura etter kinidin, Nord. med. **10**:1542-1544 (May 17) 1941.

4. Nudelman, P. L.; Leff, I. L., and Howe, C. D.: Thrombocytopenic Purpura Following Quinidine, J. A. M. A. **137**:1219-1220 (July 31) 1948.

5. Hirsch, E. O., and Dameshek, W.: Thrombocytopenic Purpura Due to Allergy to Quinidine, Am. J. Med. **9**:828-833 (Dec.) 1950.

6. Noreross, J. W.: Quinidine as a Cause of Thrombocytopenic Purpura, New England J. Med. **242**:53-54 (Jan. 12) 1950.

7. Christensen, R., and Andreason, A. P.: Quinidine Allergy, Acta allergologica **4**:37-46, 1951.

8. Sturnick, M. I.: An Unusual Toxic Manifestation of the Oral Use of Quinidine Sulfate, Am. Heart J. **24**:559-561 (Oct.) 1942.

9. Siegal, S., and Horn, H.: Quinidine Allergy, Am. Heart J. **39**:302-305 (Feb.) 1950.

10. Berley, B. S., and Saland, G.: Febrile Hypersensitivity to Quinidine Given Orally, J. A. M. A. **148**:1121-1122 (March 29) 1952.

11. Rose, O. A.; Vogel, A., and Turtz, A. I.: Drug Fever Due to Quinidine, New England J. Med. **248**:96-98 (Jan. 15) 1953.

12. Levy, R. L.: The Clinical Toxicity of Quinidine, J. A. M. A. **78**:1919 (June 17) 1922.

13. Taylor, D. R., and Potashnick, R.: Quinidine-Induced Exfoliative Dermatitis, J. A. M. A. **145**:641-642 (March 3) 1951.

14. Berman, R.; Sadoff, C. M., and Gordon, G. B.: Quinidine Intoxication Occurring During Therapy of Auricular Arrythmias, Minnesota Med. **36**:1052-1060 (Oct.) 1953.

15. Goldschlag, F.: A Case of Drug Allergy of Both Types: Fixed and Generalized Eruption, M. J. Australia **2**:501-502 (Dec. 5) 1942.

KROMAYER METHOD OF CORRECTIVE SURGICAL PLANING OF SKIN

FREDERICK REISS, M.D.
NEW YORK

The recently published article by Kurtin [1] warrants some comments. It is unquestionably to his credit that he has reintroduced a method which was known for several decades and that he has modified the abrasion technic in that instead of using burrs he has made use of stainless wire brushes.

It was Kromayer [2] who, 30 years ago, described this method, which consisted of the combination of freezing the skin with ethyl chloride, and the subsequent use of various-sized dental

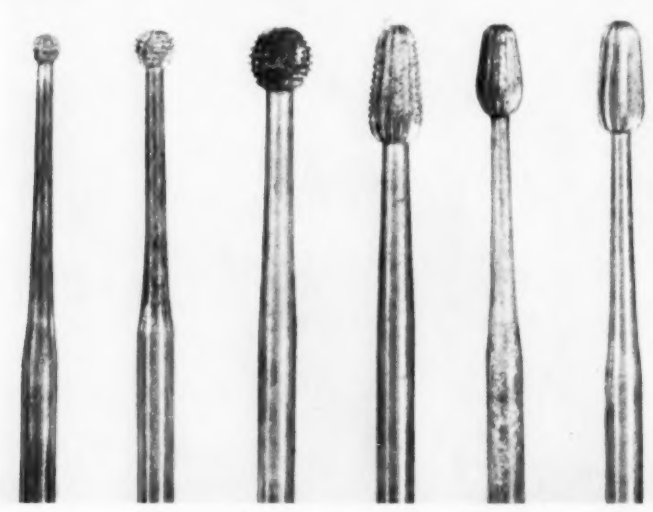


Fig. 1.—Various-sized and shaped burrs.

burrs mounted on a motor driven flexible cord (Fig. 1). This method became a recognized cosmetic procedure, and is known to most European [3] and to a good many American dermatologists. Its usefulness was proved in the treatment of some keloids, pigmented nevi, freckles, lentigines, tattoos, berloque dermatitis, and pitted scars. Kromayer also recommended this method in the treatment of the hyperpigmented borders of vitiligo.

I have had extensive experience with this method, and am convinced that the use of dental burrs has a definite advantage over the brush or sandpaper method.[4] While planing can be achieved with wire brushes and sandpaper, the small size of the burrs is more advantageous and permits greater precision and safety in the treatment of tiny areas. Furthermore, it is far easier to control the depths of abrasion with the firm burrs than with brushes or sandpaper.

Fig. 2.—Various-sized punches.

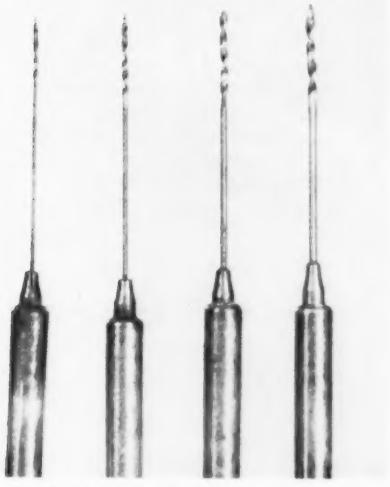


Fig. 3.—Reamer-like needles.

It may be of interest to the readers to know that Kromayer also constructed various-sized punches (Fig. 2), which are quite useful in the removal of small nevi, and furthermore, reamer-like needles (Fig. 3), which are recommended for the removal of milia and inspissated comedones.

870 Fifth Ave. (21).

REFERENCES

1. Kurtin, A.: Corrective Surgical Planing of Skin, A. M. A. Arch. Dermat. & Syph. **58:** 389, 1953.

2. Kromayer, E.: Die Behandlung der kosmetischen Hautleiden unter besonderen Berücksichtigung der physikalischen Heilmethoden und der narbenlosen Operationsweisen, Leipzig, Georg Thieme, 1923, p. 15.

3. Volk, R., and Winter, F., editors: Lexikon der kosmetischen Praxis, Vienna, Springer-Verlag, 1936, p. 545.

4. McEvitt, W. G.: Treatment of Acne Pits by Abrasion with Sandpaper, J. A. M. A. **142:**647, 1950.

Correspondence

NAEVUS SYRINGOADENOMATOSUS PAPILLIFERUS

To the Editor:—In his very interesting and informative treatise, "Life History of Naevus Syringoadenomatosus Papilliferus," which appeared in the A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY very recently (**69**:305 [March] 1954), Hermann Pinkus, on page 318, attributed the following claim to me: "The combination of naevus sebaceus with papilliferous syringoadenoma has occasionally been claimed to be exceptional (Grund [22])." This statement undoubtedly refers to an article written by me which described such an instance and which, in addition, reviewed related and similar cases seen both here and abroad (Grund, J. L.: Syringocystadenoma Papilliferum and Nevus Sebaceus [Jadassohn] Occurring as a Single Tumor, A. M. A. ARCH. DERMAT. & SYPH. **65**:340, 1952).

An examination of the comments and conclusions of my report, however, admits only of an exactly opposite impression, namely, that the concurrence of syringocystadenoma papilliferum and the collections of immediately adjacent large groups of sebaceous glands, rather than exceptional, is common. I wrote the following: "Their not uncommon combined presence (referring of course to syringocystadenoma papilliferum and nevus sebaceus) as one tumor is, I believe, significant and important in connection with the possibly correct appraisal of their pathogenesis." This impression was later repeated in the reporting of a somewhat similarly related instance in which again, in addition to other features, many large groups of sebaceous glands were a prominent accompaniment of the syringocystadenoma papilliferum (Grund, J. L., and Folan, D. W., Jr.: Syringocystadenoma Papilliferum, Nevus and Sebaceous and Basal-Cell Epithelioma [with features of Epithelioma Adenoides Cysticum and Syringoma]: Their Concurrent Presence in a Single Tumor. Report of a Case, *Urol. & Cutan. Rev.*, **55**:707, 1951).

J. L. GRUND, M.D.
18 Willard Road
Brookline 46, Mass.

REPLY TO DR. J. L. GRUND'S LETTER

To the Editor:—Dr. Grund's letter calls my attention to one of those errors that seem to creep into a paper in spite of all careful proofreading. The reference: "(Grund [22])" should have been placed, not where it is, but at the end of the following sentence, which reads in part: ". . . . . the presence of more or less malformed pilosebaceous complexes . . . furnishes the hamartomatous foundation in which the adenoma develops." At this point reference to Dr. Grund's paper gives him credit for what he actually brings out in his comment. I regret that misplacing the reference has reversed its meaning.

HERMANN PINKUS, M.D.
12 E. Fourth St.
Monroe, Mich.

DERMATOLOGICAL DESCRIPTION

To the Editor:—Any suggestions aimed at the simplification of dermatologic nomenclature or description would be welcome. I am therefore submitting the following suggestions:

When describing a dermatosis as "secondarily infected" or "impetiginized," why not simply insert the prefix "pyo" before the diagnosis? e. g.: pyocontact dermatitis; or pyoseborrheic dermatitis; or pyoeczema.

Also, when there is absorption from the primary site, or autosensitization, one can simply insert the suffix "id," e.g.: contact dermatid; or seborrheic dermatid; or eczematid.

When both secondary infection and absorption phenomena are present, one can simply state: pyocontact dermatid; or pyoseborrheic dermatid; or pyoeczematid.

We are thereby enabled to convey in one word, or simply by the addition of one or two syllables, a definite dermatologic picture.

MILTON S. HARTMAN, M.D.
711 Bushwick Ave.
Brooklyn, N. Y.

Society Transactions

CHICAGO DERMATOLOGICAL SOCIETY

Samuel J. Zakon, M.D., *President*

Irene Neuhauser, M.D., *Secretary*

Oct. 21, 1953

Hemosiderosis, Stasic Dermatitis, and Polycythemia Vera. Presented by Dr. Samuel M. Blueefarb, Dr. A. Goldberg, and (by invitation) Dr. Leonard Hoit.

The patient, C. R., a white woman, aged 60, was admitted on September 27. The patient has a 10-year history of dyspnea, palpitation, orthopnea, and edema of the legs and feet. She has been known hypertensive for five years, and has had an ulcer of the right foot for one year.

Three weeks before admission the patient developed a generalized itching and maculopapular rash. She gives a history of taking various proprietary laxatives and barbiturate-containing tablets, magnesium sulfate, glyceryl trinitrate, digitalis, "Stanish 17," and "Triple T" for many years.

The past history was essentially negative except for above. The family history was noncontributory.

Physical Examination: On admission the patient had bilateral stasis dermatitis, an ulcer (5 by 3 cm.) of the right leg, and an excoriated papulovesicular eruption of the legs, thighs, and lower trunk. Pulse: 108; blood pressure 180/105. Heart is enlarged to the left. In the left upper quadrant of the abdomen a small mass can be palpated. Treatment has consisted of potassium permanganate packs, 5% boric acid ointment, phenobarbital, chlorocyclizine hydrochloride (Di-Paralene), elevation of leg, and phlebotomy.

Laboratory Findings: Hemoglobin, 150%; red blood cell count 9,020,000; white blood cell count 8,650; nonprotein nitrogen 48 mg. per 100 cc.; total protein 7.2 gm. per 100 cc. Serology negative. Gastrointestinal x-rays revealed no pathology. After phlebotomy (2 pt.—946.2 cc.): hemoglobin 148%; red blood cell count 8,860,000; white blood cell count 8,000.

DISCUSSION

Dr. M. J. Reuter, Milwaukee: I am not an expert on polycythemia vera, but I would like to offer this observation that occasionally in patients with polycythemia vera you can get an acne-rosacea-like eruption. There is no particular cutaneous picture other than the color of the skin and the fact that hemorrhages into the skin are not uncommon.

Dr. Kurt Wiener, Milwaukee (by invitation): There have been described in Germany a number of cases of skin changes resembling Majocchi's purpura associated with a mild degree of polycythemia. Many cases of polycythemia have no skin manifestations. A considerable number of changes have been described associated with polycythemia, but none are obligatory. Varying degrees of redness and cyanosis, especially of the exposed parts, are common in the more severe cases.

Dr. Adolph Rostenberg Jr.: I recall some years ago Weidman and Klauder wrote an article (Arch. Dermat. & Syph. **29**:645 [April] 1939), describing acne urticata in association with polycythemia lesions. It was not a true acne in that there was a comedone, but consisted rather of an urticarial wheal with a superimposed pustule. Itching and excoriation were prominent features.

Dr. Samuel M. Blueefarb: Skin lesions associated with polycythemia vera may be divided into two groups: (1) those related to vascular distention and increased viscosity of blood, such

as purplish-red color of the skin, hemorrhagic phenomenon with resulting pigmentation, acne urticata, and rosacea, and (2) those related to organic changes in the blood vessels, such as thrombosis, ulcerated nodules on the legs, and scleroderma-like lesions. Hemosiderosis of the legs with ulceration is a common complication of polycythemia vera, and many cases of Majocchi's disease are merely cutaneous manifestations of polycythemia vera. The leg ulcer present in our patient healed as soon as the polycythemia was controlled by numerous venesections.

Seborrheic Lupus Erythematosus. Presented by DR. EDWARD A. OLIVER.

History: This 38-year-old white man was admitted to Hines Dermatological Service on Sept. 22, 1953, with a history of the development of what he terms to be a sore on the left side of his face about two months prior to admission, followed by spread of similar lesions around both ears, the base of the nose, chin, cheeks, trunk, arms, legs, and genitalia. He states that the lesions caused only slight itching, but are productive of considerable scaling. He applied medications verified to be an antifungal preparation (Asterol) and undecylenic acid as directed by a physician several days prior to admission. These medications subsequently produced no relief in the objective or subjective elements of the eruption. The patient states that he believes such medication caused crusting and oozing about the lesions on the face. There is no history of previous dermatitis. His occupation is that of a porter for a furniture company.

The patient is a native Chicagoan and his past history reveals he developed malaria while in the service in 1943, the most recent attack occurring in 1945.

Physical Examination: Examination reveals a white man of asthenic build with an obvious pigeon breast who appears to be about his stated age. One notes an erythematous eruption involving the scalp, face, trunk, and extremities. The eruption is well demarcated, and the borders are slightly raised with little, if any, tendency towards coalescence. On the scalp, there are noted two large coin-sized lesions with almost complete alopecia of the affected area. About the face, one notes small to large plaque-like lesions involving the cheeks, preauricular and infra-auricular regions extending onto the neck. Similar plaque-like areas are noted about the ala nasi, the upper lip, right side of the nose, and chin, as well as the left eyebrow. The majority of the latter lesions are covered with a yellowish or dark crust with some gross weeping and scaling. Scattered over the trunk and extremities, one notes numerous discrete lentil- to large-coin-sized, oval or round, mildly erythematous plaques productive of a fine lichenoid eruption and of a whitish scale. The scrotum and shaft of the penis are mildly erythematous and scaling.

Treatment has consisted of aluminum acetate soaks and 2% ichthyol in lipoid cream given topically throughout his hospitalization as well as 100 mg. of quinacrine (Atabrine) orally for the past week. Under such therapy, all evidences of weeping and crusting have ceased as well as scaling about the facial lesions.

Laboratory Findings: Admitting white blood cell count 12,000, with 69% neutrophiles, 31% lymphocytes, while the red blood cell count was 4,510,000, with 14 gm. of hemoglobin per 100 cc. Urinalysis revealed a faint trace of albumin and 10 red blood cells per high-powered field. Remainder of the routine laboratory data was noncontributory. Skin biopsy was obtained with a 4 mm. punch from the lesion on the left side of the neck and is presented for evaluation.

Subacute Discoid Lupus Erythematosus. Presented by DR. MALCOLM C. SPENCER.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: There is considerable variability in the picture of lupus erythematosus as it appeared in the several patients presented today. In the one case in which the lesions were distributed in seborrheic fashion, including the scalp, I could not rule out psoriasis. In the treatment of patients with chronic discoid lupus erythematosus, I believe quinacrine hydrochloride holds first place. Sometimes the signs of systemic lupus erythematosus are masked. If the patient has fever, arthralgia, elevated sedimentation rate, leucopenia, and a positive lupus erythematosus phenomenon, I use these drugs with caution or not at all. There are a good many patients with early signs of systemic lupus erythematosus who do well on bed rest and the administration of salicylates. The value of rest has not been emphasized enough. In the elderly patients, a mild form of treatment which is sometimes effective is the use of

strong iodine solution (Lugol's solution) by mouth. I am opposed to the indiscriminate use of cortisone or corticotropin (ACTH) in the treatment of patients merely because the diagnosis of systemic lupus erythematosus has been made. Each patient must be handled individually.

DR. LEON GOLDMAN, Cincinnati: If there was ever a question as to whether discoid lupus erythematosus can develop an extensive hyperkeratotic type of lesion, I think No. 3 illustrates that that reaction is possible. We see it not too frequently, but chiefly in colored patients.

I agree with Dr. Brunsting as far as so-called subacute and not too severe lupus erythematosus is concerned. The terms "acute," "subacute," and "chronic" refer to time relationships, not to severity. No one has told us what is the frequency of remission in patients with these milder forms of lupus erythematosus. The excellent results with various types of diverse therapies may be the results of spontaneous remission. For patients with discoid lupus erythematosus, we favor chloroquine. The reactions are certainly much less severe than with quinacrine, some vertigo, difficulty in accommodation, and weight loss. We have had no serious reactions, and a number of patients have been on maintenance dosage of 250 mg. for some months. Dr. Welsh has two reactions of leucopenia.

DR. GEORGE C. WELLS (by invitation): We also have some experience with chloroquine at the University of Chicago Clinics, having used it in the treatment of 23 cases of chronic discoid lupus erythematosus. I agree with Dr. Goldman that the results with chloroquine are as satisfactory as with quinacrine, and chloroquine has the advantages of not staining the skin and of being less toxic. Three patients in our series have complained of dizziness, but this symptom disappeared when chloroquine was discontinued. One patient while taking chloroquine developed a moderate leucopenia which has persisted in spite of discontinuing the drug, and it is uncertain whether the drug or the disease was responsible. We have been using 250 mg. of chloroquine once daily and in some cases twice daily, with over-all results comparable with those from quinacrine although the initial response is slower with chloroquine.

DR. M. R. CARO: I think Dr. Oliver's case presents a difficult problem. The lesions on the skin could be interpreted as seborrheic dermatitis, and those on the nails as psoriasis. In my opinion, however, all such cases are eventually proved to have psoriasis to account for all of their lesions. I remember several cases in which I made an unequivocal diagnosis of seborrheic dermatitis, only to have them return many years later with lesions that were unquestionably psoriasis.

DR. S. W. BECKER: I would like to make an observation that has nothing to do with lupus erythematosus. I have had several patients who as children had typical neurodermatitis and later came in with psoriasis. In one instance, the mother has psoriasis. Just because a patient comes in with psoriasis does not mean the diagnosis made previously was erroneous.

I looked at the sections from this man and they were not psoriasiform and not typical for lupus erythematosus, but they did have very definite follicular plugs which may be of significance.

DR. THEODORE CORNBLEET: It seems the belief is crystallizing that quinacrine and related drugs are the most effective ones we now have for use against discoid lupus erythematosus. Their use in systemic forms of the disease is controversial, some claiming good results, while others warn against disaster. We have not used quinacrine in systemic forms. In our series we could not tell beforehand which patient would respond best. Form of the lesions, their number or site apparently were not consistent in the groups that did or did not do well; nor could we find anything in laboratory findings or about the patients themselves to guide us to an opinion as to the prognosis to expect with the use of the synthetic antimalarials in any case.

DR. EDWARD A. OLIVER: I do not know whether my colleagues, Dr. Webster and Dr. Rostenberg, agree with this diagnosis. We first saw this man three weeks ago. At that time his skin was much more oily than it was today. He had considerable involvement of his nose and the sides of the nose extending onto the cheeks. There were patches below and behind the ears, and there were three definite spots of atrophy in the scalp. I have never seen atrophy with psoriasis. The question when we first saw him was whether this was an acute seborrheic dermatitis or a seborrheic type of lupus erythematosus. I noted the pitting of the nails, but felt that despite this condition, he did not have psoriasis.

Alopecia Ophiasis. Presented by Dr. David Omens and (by invitation) Dr. Harold Omens and Dr. Leonard Hoit.

History: The patient, L. S., an 8-year-old colored girl, first began to lose hair over the frontal area about one year ago. There was no preceding illness or trauma. Large amounts of hair would be lost in combing. The patient was taken to a local physician who gave some form of treatment, which was of no help.

The patient has had the usual childhood diseases without sequelae. The family history is noncontributory.

Physical Examination: Examination was negative except for the alopecia.

DISCUSSION

Dr. S. W. Becker: This child presented a plaque of alopecia which I think probably will fall into the group of alopecia areata, which is a functional disease. She should get the hair back. The earlier in life this occurs, the harder it is to clear up.

Dr. Kurt Wiener, Milwaukee (by invitation): I just want to recall to your mind the remark which Celsus, the Roman, made 2,000 years ago. He already found the word "ophiasis" for this particular form of alopecia in the Greek language. "The falling of hair starts on the occiput and does not exceed 2 fingers in width. It progresses with two heads beneath the ears until the two heads join on the forehead. Ophiasis is a disease which occurs almost exclusively in children and it often heals without treatment." Nothing essential has been added since.

Dr. David Omens: This child has been under observation for three months. There is no evidence of regrowth of the hair.

Systemic (?) Monilial Granuloma. Presented by Dr. Samuel M. Bluefarb, Dr. Sidney Barsky, and (by invitation) Dr. Leonard Hoit.

The patient, G. S., aged 12 years, was admitted to the Cook County Hospital on June 12, 1953. He has had monilial granulomas since 11 years of age. He had previously been treated at the University of Chicago Clinics.

Physical Examination: On admission the physical examination was negative except for a positive urinary sugar and the skin lesions which were described as heavy verrucous, hyperkeratotic lesions of the dorsal and palmar surfaces of both hands. Over the face, scalp, torso, and extremities there are erythematous papular plaques, many of which are covered with yellowish oily, hyperkeratotic crusts, of a verrucous nature.

Laboratory Findings: Hemoglobin 64%; red blood cell count 5,000,000; white blood cell count 8,900; total protein 7.1 gm. per 100 cc.; chlorides 106 mEq., sodium 140 mEq., potassium 4 mEq. per liter; nonprotein nitrogen 34 mg. per 100 cc.; fasting sugar 255 mg. per 100 cc.

The chest x-ray was negative. The patient receiving 35 units (NPH Insulin).

Many cultures from the stool, mouth, and skin lesions showed Candida albicans, and C. stellatoides. Blood, urine, and other cultures negative for fungi. Stools were negative for pathogens.

Vaccine of the two fungi given intracutaneously—0.1 cc. of 1:1,000,000 dilution negative in 24, 48, and 72 hours.

Total proteins 8.5 gm. (albumin 4.3 gm., and globulin 4.2 gm.) Cephalin flocculation 4+; thymol turbidity, 11.2 units. Gamma globulin, 2.6 gm. Vaccine was repeated three times and was negative.

Congenital Icthyosiform Erytheroderma. Tinea Capitis and Tinea Corporis—Trichophyton Violaceum. Presented by Dr. Malcolm C. Spencer.

History: The patient, R. E., a 7-year-old white girl has been presented to this society on two other occasions (February, 1950, and April, 1951).

The cutaneous manifestations have been present since early infancy. At one time (before being observed by me), she had complete hair loss not associated, however, with burrowing abscesses. Photophobia had been a problem until she was treated with water-soluble vitamin A given concomitantly with cortisone, as suggested by Webster in 1951.

During a month's trial for effect of environment in Tucson, Ariz., in the summer of 1951, the patient developed severe miliaria and secondary pyoderma. Upon returning she presented several annular lesions on body and scalp suggestive of a superficial mycosis. Culture was positive for T. violaceum, subsequently repeated and positive. Alopecia began to develop in October, 1952. This has gradually increased in area. Burrowing folliculitis suggestive of perifolliculitis capitis abscendens et suffodiens became apparent in August, 1953. Has not responded to neumerous fungicidal preparations.

Laboratory Findings: In 1950 biopsy specimens from arm "consistent with congenital ichthyosiform erythroderma" (Dr. Ginsberg); 1951—arm "consistent with diagnosis of pityriasis rubra pilaris" (Dr. Ginsberg); 1952—excrescence from forehead—verruca vulgaris.

DISCUSSION

Dr. J. Walter Wilson, Los Angeles (by invitation): (Referring to the patient presented by Dr. Bluefarb). I believe this child has two congenital anomalies, diabetes mellitus and ichthyosiform erythroderma upon which moniliasis has been superimposed. Fungi are like all other forms of life; they are always looking for a pleasant place to live. It is not surprising to me that they have discovered that the involved areas on this patient furnish them with much which they like, such as breaks in the continuity of the epidermis and exudate containing an increased concentration of glucose. I cannot conceive of moniliasis occurring and persisting in the bizzarre distribution exhibited by this patient while its favorite intertriginous sites are ignored, except because of the existence of an antecedant dermatosis with a predilection for this localization. Congenital ichthyosiform erythroderma is frequently seen in this distribution.

I consider it also extremely significant that there are some areas of the skin, in fact the majority, which have never become involved during all these years. If the disorder were simply an infection, without there being any variation in resistance of one area over another, a mere scratch would have inevitably inoculated it elsewhere.

I believe the most important feature of treatment in this case is the strict management of the diabetes, striving for even less elevations in blood sugar than ordinarily allowed. A better degree of simple cleansing of the involved areas using diluted benzalkonium chloride (Zephiran) would be of help, followed by the use of lotions or ointments as indicated, but containing nothing of plant or animal origin which might serve to nourish fungi or bacteria. Thus, I would select talc or zinc oxide to the exclusion of starch, and mineral oil and petrolatum instead of hydrous wool fat (lanolin) or vegetable oils.

I do not believe any fungicide can cure this patient unaided, and I would use fungicides only if an agent active against Candida is available which is also nontoxic and nonirritating.

It is fortunate that we have today had the opportunity of comparing this patient with the child in the case presented by Dr. Spencer which I consider to be parallel. This child admittedly has a congenital ichthyosiform erythroderma of long duration upon which has recently been superimposed a fungus infection, this time caused by Trichophyton violaceum.

Dr. Stephen Rothman: I do not see any evidence that this child is inflicted with ichthyosiform erythroderma. He was a normal child until the age of 4 and then took ill with monilial granuloma. His case was reported in detail (Archives of Dermatology and Syphilology **61**:297-310 [Feb.] 1950), and I believe we presented evidence that monilial granuloma is a disease entity in which peculiarities of the host tissues permit Candida albicans to cause granulation as contrasted with the banal superficial lesions of common moniliasis. The child's diabetes became manifest only 11 years after the onset of the disease, and our review of the literature indicates that diabetes is not a necessary condition for the development of monilial granuloma. If Dr. Wilson means that there is a predispositional factor in this case, I fully agree and would like to add that there must be such factors in all cases of moniliasis because the organism seems to be ubiquitous. But diabetes is one such factor, the intestinal disease in acrodermatitis enteropathica is another one, and both are distinctly different from the unknown predispositional factors in monilial granuloma. Ichthyosiform erythroderma cannot be a predispositional factor here because the child has none; neither had any of the patients with monilial granuloma described in the literature.

The therapeutic results achieved with fungicidin (Nystatin) are quite remarkable. The child's face has greatly improved. After taking care of this child for many years in the hospital, I can assure Dr. Wilson that with good hygiene, combined with local antibacterial and oldfashioned antifungal treatment, monilial granuloma cannot be cured.

The question whether the child has no favus has been often discussed here. In hundreds of specimens we cultured pure Candida albicans, and we also were able to show that C. albicans, does not suppress the growth of Achorion schoenleini.

DR. IRENE NEUHAUSER: When this case was first shown, at the request of Dr. Welsh, I sent some hairs and scales from the scalp to Dr. Ochoa, Chief Mycologist at the Institute of Tropical Diseases, Mexico City. Dr. Ochoa isolated Tricophyton schoenleini from the material sent to him. I, myself, was not able to isolate the organism, although I did see Trichophyton forms on direct examination. I agree with Dr. Omens that it has been possible to find typical scutula in the scalp. Although the clinical appearance has changed a great deal since originally shown, there has never been a question of congenital erythroderma.

DR. SAMUEL M. BLUEFARB: The comment made by Dr. Wilson was very interesting, since a similar opinion was given by Dr. Snapper, of our medical staff, who also believes the moniliasis to be secondary to an underlying process. This patient has received considerable therapy with diiodohydroxyquinoline, (Diodoquin), stilbamidine, diethylstilbestrol, chlorotrianisene, (Tace), and a new fungicidal agent, fungicidin (Nystatin) was recently used. Although sufficient time has not elapsed to make a definite statement, this latter therapy appears to be the most promising.

DR. NEUHAUSER: I wish to emphasize the importance of looking for some systemic disease in all these cases of persistent Monilia infection. I recall a case sent to me by Dr. Finnerud and Dr. Szymanski with an extensive resistant moniliasis involving the hands, feet, and mouth. According to Dr. Rothman, who saw the patient later, she suddenly developed tuberculous adenitis and died from tuberculous meningitis. I think these cases of resistant moniliasis are related to some systemic pathology.

Papulonecrotic Tuberculid Treated with Isoniazid (Isonicotinic Acid Hydrazide). Presented by DR. ROYAL E. IHRKE and (by invitation) DR. B. J. PASS.

History: D. S. is a 15-year-old colored girl who was first examined at the Northwestern University Department of Dermatology, May 5, 1953. There were lesions in varying stages of development on the upper and lower extremities and on the trunk. They start as deep nodules which come to the surface, crust, scale, and eventually heal, leaving depressed hyperpigmented scars. The mother states that the patient had been ill, as a child, and had been hospitalized at the Cook County Hospital running a fever for months and that a specific diagnosis had not been made.

Physical Examination: The medical department examination was negative. She was placed on calciferol, 100,000 units per day from June 17 to Aug. 4, 1953, without any results. There were no reactions. New lesions appeared during the period she was taking calciferol.

Isoniazid, 50 mg., t.i.d., was started on Aug. 18, 1953. Within two weeks, new lesions stopped appearing and only hyperpigmented lesions are present. She is still on medication.

Laboratory Findings: Urinalysis was normal. Red blood cell count 4,590,000; hemoglobin 13.2 gm. per 100 cc.; white blood cell count 5,300; sedimentation rate 13 min. Chest x-ray normal. Mantoux 1:1,000 was strongly positive.

The biopsy examination was reported as being consistent with papulonecrotic tuberculid.

Sarcoid Clinically—Tuberculosis Cutis Histologically. Presented by DR. JAMES R. WEBSTER, DR. STANLEY HUFF, and (by invitation) DR. LEONARD HOIT.

History: The patient, E. B., a 71-year-old colored woman was admitted Sept. 21, 1953. She first noticed patches on her ears and on the back of her neck about three weeks before admission. The involved areas were pruritic, tender to palpation but not painful. The lesions first appeared as flesh-colored nodules which later coalesced. She had scratched the involved areas a great deal.

The patient states that about one year ago she had several "tumors" removed from the dorsa of the hands and feet and from the back. She describes these as being hard, raised, nonulcerated bumps, which were different from the lesions at present.

The fingers showed no cystic changes.

Laboratory Findings: Hemoglobin 84%; urinalysis negative; white blood count 6,750; total protein 7.2 gm. per 100 cc.; (albumin 5 gm., globulin 2.2 gm.); chlorides 102 mg., sodium 144 mg., potassium 19.5 mg. per 100 cc.; CO_2 52 vol. %.

Chest x-ray showed hilar adenopathy compatible with Boeck's sarcoid.

DISCUSSION

DR. J. WALTER WILSON, Los Angeles (by invitation): Dr. Obermayer and I reported the first instance of lupus vulgaris treated with isoniazid. After 42 years of continuous involvement, our patient was clinically cleared in 15 weeks on this therapy. However, we were then still able to demonstrate tubercle bacilli by biopsy studies. I understand that other investigators have also had this experience. All such patients must be closely watched for recurrence.

DR. GEORGE C. WELLS (by invitation): The British reports on the use of isoniazid in the treatment of lupus vulgaris are enthusiastic. We have recently seen an excellent result in a woman with obstinate lupus vulgaris of the thigh, where after about three months of treatment with isoniazid, biopsy of a lesion showed complete dissolution of microtubercles. The question is whether this drug should be used alone, or, whether, because of the potentiality of the tubercle bacillus for developing resistance, isoniazid should be given concurrently with streptomycin or paraaminosalicylic acid? At present I favor giving isoniazid along with streptomycin and dihydrostreptomycin.

Case for Diagnosis. Parakeratosis Variegata? Presented by DR. J. B. HOWELL.

History: Patient, E. D., has had an eruption for approximately 11 years. He thinks the present eruption commenced on the backs of the fingers in 1942. In approximately one year the eruption spread to involve the forearms and face. A gradual extension to involve the entire face, neck, and arms continued until 1948. The eruption cleared almost completely during 1948 and 1949 while patient was in the Army. Three months after discharge from the Army in 1949, the eruption on the forearms, backs of the hands, and face became prominent.

The patient worked as a mechanics helper before entering the Army. Since military service he has worked as a tool and die maker. Oil is contacted at work and in a machine shop which the patient has as a hobby after work.

Physical Examination: Physical examination by an internist in May, 1953, was essentially normal. Blood pressure was 116/76. The liver and spleen were not palpable.

The appearance of the skin has been essentially the same each day with the exception of the appearance of new areas over the thighs and abdomen. There is and has always been prominent follicular hyperkeratosis over the dorsa of the proximal phalanges. The forearms and arms present a striking reticulated erythematous eruption with moderate scaling. There is a dusky brown reticulated eruption over the face and neck with considerable melanosis of the face. New areas have been noted over the thighs as a transient erythema. A reticulated erythema has appeared over the abdomen recently. This eruption is now assuming the character of the other areas.

A five months' course of 200,000 units of vitamin A (Aquasol A) resulted in questionable improvement. Since Sept. 1, 1953, 100,000 units of vitamin D have been taken daily. For six to eight weeks 5% monobenzone (Benoquin) ointment has been used over the neck and forehead, with some improvement of melanosis.

Laboratory Findings: Kline test was negative. Urinalysis was normal. Hemoglobin 109.3%; red blood cell count 4,950,000; white blood cell count 7,500; differential count normal. Sedimentation rate 6 mm. in one hour. Serum albumin 4.0 gm. per 100 cc.; globulin 2.85 gm. per 100 cc.

X-ray examination of the chest and kidney-ureters-bladder x-ray examination were negative. A Congo red test was done on the left forearm and was negative.

Biopsy of forearm in January, 1953: The liquefaction degeneration and the keratotic plugging support a diagnosis of pityriasis rubra pilaris, but this is the first case of this disease, if it is that, in which there is no evidence of parakeratosis. The follicular plugging and the liquefaction degeneration of the basal layer do not fit parapsoriasis variegata or other forms of parapsoriasis.

Biopsy of forearm in August, 1953: The epidermis is hyperkeratotic; the granular layer is unevenly thickened, the rete partly atrophic, partly slightly hypertrophic, with irregular elongation of the rete ridges. There is some spotty loss of basal cells over areas of dermal infiltrate, and there are a few grain-like (individually keratinized) cells in the rete. Pigmentation is spotty, and some pigment has been carried down into the corium. The corium contains spotty perivascular infiltrate, which is quite unevenly distributed in the subpapillary layer. In some spots it hugs the epidermis almost as in lichen planus. It is particularly pronounced around hair follicles, which are wide with keratotic plugs. In addition, there is much hyaline material in the form of small globes beneath the epidermis and around hair follicles. This material gives the staining reactions of amyloid (yellowish orange in van Gieson sections, light blue in orcein-Giemsa sections).

Parapsoriasis. Presented by DR. A. BUCHHOLZ.

History: E. J., a 6-year-old boy, has a history of an eruption without objective symptoms, involving the trunk, face, arms, and legs, of one year's duration. The general health has been good, and there are no obvious systemic disorders. The patient first presented irregular-sized papulosquamous lesions covered with a silvery scale that were confluent on the trunk.

Treatment consisting of coal tar derivatives, salicylic acid, and ammoniated mercury has not altered the clinical course.

Laboratory Findings: Examination of a section from an arm lesion shows slight thickening of the scale, mild acanthosis with intracellular edema, and few inflammatory cells scattered throughout the epidermis. Mild inflammatory reaction consisting of lymphocytes, plasma cells, and histiocytes surrounds the superficial vessels in the corium.

Pityriasis Lichenoides et Varioliformis Acuta. Presented by DR. EDWARD A. OLIVER.

History: This 37-year-old white laboratory technician presented herself to the dermatological service of this institution about one month ago with the complaint of the appearance of numerous discrete, rose-colored, nonpruritic papules on the trunk and extremities, more pronounced initially on the abdomen, of a week's duration. She gave a history of the appearance of a mild diarrhea with vague constitutional symptoms for several days prior to the advent of the eruption. She is married, has no children, and there is no history of similar eruption in the family. Past history is noncontributory, with the exception that the patient has been treated for the past three months for a contact dermatitis of the right hand due to a primary irritant.

Physical Examination: When originally seen the patient presented discrete, brownish-red, slightly infiltrated papules on the trunk and extremities, being more numerous on the abdomen. One week later there appeared discrete lentil-sized varicelliform vesicles and numerous oval, papulosquamous lesions with a blackish-brown crusting. This polymorphic eruption has persisted as such until the present time.

Treatment has consisted only of ultraviolet therapy once weekly to the affected areas for the past three weeks.

DISCUSSION

DR. EDWARD A. OLIVER: The case of Dr. Howell's patient is a most interesting one. I talked with this young man for a considerable time. He told me he had been at this particular type of work for 11 years, and that he developed this eruption 6 months after beginning this work. He uses cutting oils and is constantly in contact with them. It appeared to me to be a melanosis, the result of contact with these oils. There were lesions on the dorsal aspects of his fingers and follicular plugging, suggestive of pityriasis rubra pilaris, but there were no other symptoms to substantiate that diagnosis. He also had small lichenoid lesions on the forearms which had a sheen, were papular and suggestive of lichen planus.

In view of the fact that he has had this for 10½ years, ever since he began this work, I believe we should consider this an occupational dermatitis due to oil or tar.

DR. HARRY R. FOERSTER, Milwaukee: In Dr. Howell's case, the melanosis of the face could be related to his occupation, by oil contacts having caused photosensitization, though in such cases the pigmentation usually has a grayish hue, but I do not believe the eruption on the upper extremities to be of such origin. He has had this latter eruption for 12 years, which is too long for lichen planus. A diagnosis of parapsoriasis lichenoides of Brocq (parakeratosis variegata) is tenable for the lesions. The plugging of the pores on the dorsa of the fingers suggests consideration of pityriasis rubra pilaris, but there are no other features of that disease. These plugs could have resulted from occupational oil exposures.

I accept the presenter's diagnosis for the inflammatory eruption on the extremities.

DR. ADOLPH ROSTENBERG JR.: I would like to say a few words about parapsoriasis in general and the Mucha-Habermann syndrome in particular. Brocq took a group of miscellaneous dermatoses and grouped them together and called the group parapsoriasis. I think everyone is beginning to doubt that this group presents an ertity.

In the September issue of the *British Journal of Dermatology*, there is an excellent article by Ingram on the parapsoriasis group. Classically, parapsoriasis has been divided into three groups (1) P. guttata, (2) P. en plaques, and (3) P. lichenoides. Now the synonymity has served to cause much confusion, for parapsoriasis guttata and pityriasis lichenoides are the same, whereas parapsoriasis lichenoides and parakeratosis variegata are the same. It is important not to confuse pityriasis lichenoides and parapsoriaisis lichenoides, as these are probably quite different conditions with entirely different prognoses. Finally, to add to the confusion, there are guttata forms of parapsoriasis en plaque, but these again are not to be confounded with parapsoriasis guttata for the reasons just given.

What is the Mucha-Habermann syndrome? I do not think there is any doubt that the case shown by Dr. Oliver belongs to that group. The problem, though, is what is the nature of these cases? In this country, the first report was by Senear and Oliver in 1931 (ARCH. DERMAT. & SYPH. **23**:12 [Jan.] 1931). It was a very good article, and there was an interesting discussion of it. Pusey, Politzer, and Highman all doubted that the syndrome was parapsoriasis. Wise thought the syndrome was a form of parapsoriasis, but he did not give any reasons as to why. As a matter of fact, in closing, Dr. Senear said, "We were unable to convince ourselves that this disease is a form of parapsoriasis; but the name under which we reported these three cases is the name which was used throughout the literature and it seemed to us to describe fairly well the appearance of the lesions."

Since that time I do not think there is doubt that the Mucha-Habermann syndrome is an acute form of pityriasis lichenoides, but the important concept is whether either the acute or chronic forms have anything to do with the other conditions labeled parapsoriasis? Ingram thinks they do not, and his reasons seem cogent to me. If this is true, it is important that the pityriasis lichenoides chronica or acuta be called only by this name and not by any of the synonyms in which the word parapsoriasis is employed, for this would only serve to perpetuate the confusion and cast an ominous prognostic shadow over what is otherwise a relatively benign condition.

DR. EDWARD A. OLIVER: I was very much interested in Dr. Rostenberg's remarks about this peculiar disease. I was present at the meetings he has mentioned and heard the same objections to classifying it as a form of parapsoriasis that he has advanced. When Dr. Senear and I presented our first cases at a meeting of this Society in 1929, there was considerable discussion. Dr. Pusey was much displeased that anyone should spoil the concept previously held about parapsoriasis.

The name was originally given it by Habermann in 1926, but it was originally described by Mucha in 1916. Since that time, many papers by European dermatologists have appeared on this subject and all have given it this name.

When we read a paper entitled "Pityriasis Lichenoides et Varioliformis Acuta" before the American Dermatological Association in 1930, the discussion was quite animated. Dr. Pollitzer, Dr. Pusey, and Dr. Highman all objected to including it in the Parapsoriasis group. Dr. Highman in discussing the paper said, "I think that Dr. Senear and Dr. Oliver are too modestly succumbing to the European literature. I think this is a type of disease *sui generis*, which has no more to do with parapsoriasis than the pityriasis or psoriasiform type of dry eczema has to do with psoriasis. The mere fact of the similarity of the lesions in the two diseases, as we know, establishes no relation between the two."

In his discussion, Dr. Fred Wise made the suggestion that we call this disease parapsoriasis varioliformis. That does seem a better name.

I do not know whether this is a form of parapsoriasis or not. I do, however, believe that in the past it was very difficult to differentiate this disease from secondary syphilis. Now that we know the symptoms, it is easily recognizable. The discussion as to whether it is a form of parapsoriasis or not, I will leave to our younger dermatologist to decide.

DR. THEODORE CORNBLEET: I notice that Dr. Howell's patient has not only a follicular keratosis on the backs of the fingers but an erythematous eruption on the forearms and arms. I thought of the possibility of pityriasis rubra pilaris and also of an occupational dermatitis due to such things as oil and tar.

DR. J. B. HOWELL: He contacts oils; this might explain the melanosis and follicular plugs over the backs of the fingers.

Ocular Pemphigus. Presented by DR. GEORGE C. WELLS (by invitation).

History: Mrs. V. C., 67-year-old Negro widow, first noticed soreness in the mouth in August, 1952. Before that time her health had been good.

The soreness on the right side of the palate and gum was first noticed when her denture rubbed, but in spite of leaving out the dentures, the soreness persisted. She used to smoke but has not done so since her mouth became sore. She was in the habit of taking a laxative containing phenolphthalein (Feenamint) for constipation, but has not taken any for 12 months.

This patient has been under observation for about one year during which time fresh bullae and erosions have been seen in the mouth from time to time and the inflamed patch on the palate and gum has never disappeared. Any fresh activity is always within the confines of the original lesion of the right side palate and gum. Some relief is obtained from alkaline mouth washes and local applications of methylrosaniline chloride (gentian violet) or of chlortetracycline (Aureomycin). She had not complained of her eyes until about four weeks ago.

Physical Examination: General physical examination was negative, apart from hypertension (blood pressure 180/115).

On the right side of the palate and adjacent gum margin, there is a depigmented erythematous area showing superficial erosions.

Right Eye: There is a ribbon of fibrous tissue connecting the bulbar conjunctiva with the conjunctiva of the lower lid visible when the lower lid is pulled down.

Left Eye: There is redness and chronic inflammatory reaction of the conjunctiva. Both upper lids show xanthelasma.

Laboratory Findings: Urinalysis was normal. Wassermann and Kahn tests were negative. White blood cell count 6,700; differential: polymorphonuclears 49%; lymphocytes 43%; monocytes 5%; eosinophiles 3%.

X-ray examination of the chest was negative. X-ray examination of affected region of palate showed no bone disease.

Culture from palate showed a mixed pyogenic flora.

Biopsy specimens from the palate are presented. The epithelium is edematous and partly separated from the papillary region. The subepithelial connective tissue shows edema and a fairly dense chronic inflammatory infiltrate consisting of lymphocytes, plasma cells and a few eosinophiles.

DISCUSSION

DR. GEORGE C. WELLS (by invitation): I think that this case is quite typical of ocular pemphigus. It seems quite clear that this disease is entirely distinct from true pemphigus. Cases of ocular pemphigus may be followed for years without there being any impairment of general health, and the lesions consistently do not show acantholysis. In this case, the only lesion complained of initially was in the mouth, and it was a year before a conjunctival lesion became sufficiently active to cause symptoms. This same point is emphasized by Church and Sneddon (*Brit. J. Dermat.* **65**:235, 1953) who found other lesions, usually in the mouth, had preceded

ocular lesions in five cases out of seven. These authors maintain that in the oral mucosa the combination of "blisters," scars, and white streaking is pathognomonic of "ocular pemphigus" as it affects the mouth.

Comedo-Plugs Associated with Pregnancy. Presented by Dr. Stephen Rothman and (by invitation) Dr. Edward H. Ferguson.

History: E. R., a 38-year-old white housewife, has been pregnant three times. Her first pregnancy in 1949 terminated in two months with a spontaneous abortion. Her second pregnancy terminated in 1951 with a premature delivery of a 7½-month infant who died several hours later. During both pregnancies she received some kind of hormone therapy, and in both instances she developed an eruption on the face similar to the present one. In the second pregnancy, the chest and shoulders were also involved, and there was some facial hypertrichosis. The eruption cleared completely after the first pregnancy and almost completely after the second. She was delivered on Sept. 26, 1953, of a 2,000 gm. girl, who is now alive and well. This third pregnancy was complicated by a mild hypertension, and during this pregnancy, when no hormones were given, the eruption again developed and became progressively worse.

One younger sister had a somewhat similar eruption on her face during pregnancy. There is a familial history of red hair and freckling.

Physical Examination: The results of physical examination were within normal limits. On the face, mainly on the cheeks, there are numerous, rounded, pointed, and flattened yellow follicular papules. From most of these a thick, yellowish, cheese-like material can be expressed.

Laboratory Findings: Laboratory tests were within normal limits.

A punch biopsy was taken on Oct. 7, 1953, from the right side of the face near the angle of the mandible. In the center of the section there is a flask-shaped cavity opening onto the surface. The cavity contains keratin and is lined by stratified squamous epithelium.

DISCUSSION

Dr. Theodore Cornbleet: I have seen patients with this condition before—one, not so long ago, with less involvement, though. The patient said her lesions are more numerous and conspicuous during pregnancy. The number of purplish striae is most unusual even during pregnancy. Her face is distinctly hyperpituitary-like in appearance, and her hands, too, are large for a woman. I believe endocrine studies of this woman would be found profitable and that the 17-ketosteroids will be found considerably elevated.

Dr. Stephen Rothman: It is remarkable that this condition is not mentioned in the literature though probably it is not unique. This patient also has more striae than found in the normal pregnant woman.

Xanthoma Tuberosum Multiplex. Presented by Dr. Wadter Klak (by invitation) and Dr. George C. Wells (by invitation).

DISCUSSION

Dr. George C. Wells (by invitation): We were very much impressed by the marked fall in serum lipids and serum cholesterols while this man was on a mild reducing diet of 1880 calories, with no special limitation of fat or cholesterol. We think probably there is some softening of the lesions, but it is too early to say whether there is any real regression.

Prurigo Nodularis. Presented by Dr. Edward A. Oliver.

History: This 33-year-old white man was admitted to the Hines Dermatological Service on Oct. 6, 1953, giving a history of what he terms to be "knotty sores" developing in 1949 in the scalp, followed by the appearance of similar lesions on both legs, arms, neck, and upper portion of the back. Such lesions have persisted in spite of various and sundry types of topical and systemic medication in the past four years. He states that they are very pruritic in the evenings. He is a native of Armenia and his occupation is variable, that is, steel painter, cabby, trucker, and odd jobs. There is a history of an adjustment problem in his home life. Past history

reveals that in 1943, while in the service in the South Pacific, the patient had a previous dermatitis, termed impetigo, which resolved under three weeks' therapy and was followed by scarred areas on his back.

Physical Examination: Examination reveals a well-developed, moderately nourished, white man, of questionable average intelligence, who did not appear to be acutely ill. One noted numerous small to large pea-sized, round, oval, or oblong, firm and light pinkish nodules on the scalp, neck, upper portion of the back, forearms, arms, pubic area, and thighs. The majority of the lesions were excoriated, crusting, and scabbed. They were noted to be more numerous on the anterior surface of both legs, showing a tendency toward a linear arrangement. Several pale and slightly depressed, pea-sized, pitted, atrophic areas were noted about the upper back. Bilateral shotty femoral lymph nodes were palpable on admission.

Laboratory Findings: Not significant. Routine chest x-ray was normal. A 4-mm. punch biopsy of a skin lesion of the right leg has been performed on Oct. 8, 1953, and has been presented for interpretation. If available, a previous punch biopsy taken at the Veterans Administration Regional Office in April, 1953, will likewise be presented.

Treatment has consisted of 5% salicylic acid ointment applied to the affected areas twice daily since admission. At the present time the patient states that the lesions are less pruritic, and objectively one notes considerable dimmution of excoriation, crusting, and scabbing over the surface of the lesions. The lesions themselves have developed a bluish tinge with a slightly verrucous surface since admission.

Case of Prurigo Ferox of Long Standing. Presented by DR. FRANK J. KENDRICK.

History: The patient, I. J., a 42-year-old white man born in the United States, has a generalized dermatitis present, he states, since birth.

Physical Examination: The skin is generally pigmented, rather leathery, and lichenified, with many fine depigmented macules on forearms chiefly. The patient states these depigmented areas are the result of trauma over the years. He has very little hair anywhere on his body. He shaves every third or fourth day.

Dr. Goecherman diagnosed the case as prurigo ferox in 1924.

Laboratory Findings: Blood examination and urine were both negative.

Microscopic section as shown. Dr. Wilbert Sachs' description of the pathology is as follows:

Oct. 13, 1953: The superficial vessels are dilated, and about them is a focal reaction composed of simple cells. The cutis shows edema of the collagen bundles. The epidermis is mildly acanthotic and dry, and in some areas there is pigment in the lower part. The picture is that of aneurodermatitic reaction with long-standing edema of the cutis. These findings would fit in with a prurigo type of lesion such as prurigo ferox.

DISCUSSION

DR. STEPHEN ROTHMAN: Prurigo ferox as described by Hebra and as it was seen in Europe until shortly after the First World War was characterized by the development of extremely itching papules, predilectionally on the extensor aspects of the extremities. These papules were short-lived because they were torn off by the scratching fingernails. Marked generalized lymphadenopathy set in soon after the onset.

I haven't seen this entity since the middle twenties and certainly did not come across a single case in the United States in the last 15 years. In the case presented, there is only moderate itching; the patient is not disturbed in his sleep every night by pruritus, and he has no lymphadenopathy. Therefore, I cannot agree with the diagnosis.

DR. M. R. CARO: I am not going to come to Dr. Oliver's defense; I am merely offering my sympathy. The cases I have seen of prurigo nodularis do not respond well to any type of treatment.

DR. EDWARD A. OLIVER: I thought Dr. Kendrick's case was very interesting. I agree with the diagnosis, though I had never seen it in that young an individual. It is rather unusual.

About our case of prurigo nodularis, this man has suffered from this disease for seven years. None of the original lesions have disappeared, and he continually develops new ones. The pruritus is intense. I realize that some European dermatologists believe this to be an atypical neurodermatitis, but I feel certain this is a case of prurigo nodularis.

Urticaria Pigmentosa. Presented by DR. S. W. BECKER.

History: The patient, M. J. W., a 14-month-old girl, had a "rough discolored skin" when she was born. She had no symptoms until the hot weather of 1953, at which time the lesions became more prominent. She itched and scratched, thereby producing linear wheals in the involved portions. She also developed "blisters," some of them in areas where it would be difficult to reach, such as the interscapular region.

Physical Examination: When first seen on July 7, 1953, she presented a few patches of normal skin on the trunk. Most of this region was involved in a buff-colored thickening in which the skin appeared "padded." She had linear wheals at sites of scratching. The eruption was most severe on the trunk and proximal portions of the extremities. Diagnosis was made of maculonodular urticaria pigmentosa.

Laboratory Findings: Biopsy specimen was removed from a "padded" area on the left thigh. The papillae were packed with cells with basophilic cytoplasm, which was metachromatic on special staining. The superficial dermis contained decreasing numbers of such cells, largely perivascular. The silver method showed mild melanosis in the epidermis, with a few dendritic cells.

Roentgen study of the entire skeleton revealed no gross pathological changes. There is no family history of similar disorder.

Microscopic sections are presented.

DISCUSSION

DR. S. W. BECKER: This is a classical case of the so-called papular variety of urticaria pigmentosa, present at birth. Some recent work (Antalóczy, Z.; Nékám, L., and Komáromi, J.: Liberation and Inhibition of Heparin in Urticaria Pigmentosa, *Hungarian Med. Weekly* **91**:1134, 1950; abstracted, *Excerpta Med.* XIII **5**:1045, 1951, and Riley, J. F.: Histamine in Tissue Mast Cells, *Science* **118**:332 [Sept. 18] 1953), has shown that, in addition to heparin, histamine is liberated from the mast cells by mechanical irritation. The pigmentation in the basal portion of the epidermis has never been satisfactorily explained. The disorder could be better called "mastocytosis," in line with the designation "mastocytoma" for mast-cell tumors.

The macular variety of urticaria pigmentosa starts fading out at puberty in most instances. The papular variety shown by the patient today, was still prominent at the age of 27 in a patient presented by Kahn and myself, (Kahn, D. and Becker, S. W.: A Case for Diagnosis [Systemic Nevus?] ARCH. DERMAT. & SYPH. **45**:995-996, 1942), on whom Dr. Caro made the diagnosis of urticaria pigmentosa. It seems that we do not have much to promise this patient.

DR. THEODORE CORNBLEET: Animals such as rabbits whose tissues show few mast cells are generally susceptible to laboratory production of atherosclerosis; those animals, on the contrary, with liberal numbers of such cells resist it. It would be interesting to see whether cholesterol injection of this child's skin would attract mast cells. The heparin granules of these cells in the lesions of urticaria pigmentosa show no evidence of blood anticlotting capacity; perhaps some enabling co-substance is lacking or some restraining material is present to interfere.

Acrodermatite Continué. Presented by DR. FRANCIS E. SENEAR and DR. JOHN B. HAEBERLIN JR.

History: The patient, J. M., aged 50, was first admitted to the Dermatology Ward at the University of Illinois Research and Educational Hospital on April 23, 1951. The patient, an iron worker, was in good health until May, 1950, except for a bowel resection seven years previously for adenocarcinoma of the colon.

Two weeks after using penicillin lozenges for a sore throat, he developed a tender fissured tongue and a localized dermatitis on the right foot and in the groin. Later he developed a high fever, which was followed by generalized erythema, itching, and exfoliation, which soon became pustular on the palms and soles and had a psoriasiform appearance in the lesions on the back.

Repeated biopsies of this and other later psoriasiform patches on back and extremities revealed only a picture of nonspecific dermatitis. Chlortetracycline (Aureomycin) taken during this period only increased the fever. He was hospitalized at Presbyterian Hospital in July, 1950, for seven weeks. During his stay there he received corticotropin (ACTH) intramuscularly, chloramphenicol (Chloromycetin) and chlortetracycline orally, and many local medications. While in the hospital he had an attack of coronary thrombosis. The generalized eruption gradually cleared entirely and the feet improved markedly. He was discharged, and 48 hours later the pustular eruption recurred on his feet and hands. On Oct. 27, 1950, he was admitted to the Evangelical Hospital with a severe exfoliative dermatitis with lymphadenopathy. The generalized exfoliation subsided, and a painful, pustular eruption reappeared on the hands, feet and tibiae. In spite of numerous therapeutic measures, his condition remained unchanged.

Physical Examination: On April 23, 1951, he was admitted to the University of Illinois Research and Educational Hospital. A painful pustular dermatitis was present on the palms, soles, and anterior surfaces of the lower part of the legs. Circumscribed, erythematous, scaly lesions were present on the elbows.

On July 2, 1952, a gastroenterostomy and a vagotomy were done because of a persistent duodenal ulcer. He again had surgery on July 15, 1952, for a small bowel obstruction due to adhesions.

Laboratory Data: Repeated urinalyses have shown a persistent albuminuria with occasional red blood and white blood cells. Renal function tests revealed renal damage. Repeated white cell counts varied from 10,600 to 14,500, with normal differential counts. There has been persistent anemia, increased sedimentation rate, and elevated nonprotein nitrogen. Other blood chemistry studies have given normal results.

Electrocardiogram was normal. Roentgen studies revealed normal chest, demineralization of small bones of hands and feet, and an active duodenal ulcer. Sternal marrow was normal.

Repeated blood cultures were negative, except on July 27, 1951, when hemolytic and nonhemolytic Staphylococcus aureus were found. Urine culture: Hemolytic Staphylococcus aureus, micrococcus, pseudomonas aeruginosa (B. pyocyaneus). Skin cultures: pustule—nonhemolytic Staphylococcus aureus and micrococcus. Biopsy examinations: Skin of right elbow and skin of leg was consistent with infectious dermatitis.

During the hospital stay there were repeated acute outbreaks with fever, exacerbation of the pustular elements on the hands, feet and legs, and at times a more or less generalized erythema of toxic type.

DISCUSSION

DR. RUBEN NOMLAND, Iowa City, Ia.: I think this would qualify for the diagnosis under which it was presented. I do not know how you should look at the syndrome, but over a period of 10 or 15 years we had a nurse with this disease, with loss of the fingernails, patches of oozing dermatitis, and pustules. She had flare-ups and remissions and would be in the hospital for months at a time, occasionally responding, but finally she died.

At autopsy it was found that the entire pancreas was nearly replaced by fatty tissue. I would recommend that this man have a check-up as to the possibility of serious systemic disease. He had an operation for carcinoma of the sigmoid seven years ago, and it is barely possible that some internal derangement may explain the undue sensitization to what looks like a pyogenic infection.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Acrodermatitis continua Hallopeau is a rare disorder, and it is quite possible that we are dealing with the syndrome in this particular case. I do not know any measures of treatment that are uniformly effective, although quinacrine could be tried. In dermatitis repens I agree with Combes that quinacrine is sometimes quite helpful.

Pituitary Basophilism in Acanthosis Nigricans, Juvenile Type: Autopsy Report.
Presented by DR. STEPHEN ROTHMAN.

In this society, the possible pituitary origin of the juvenile type of acanthosis nigricans was discussed several times in the last 10 years (ARCH. DERMAT. & SYPH. **48**:468, 1943; **52**:59, 1945, and **63**:80, 1951). The patient whose autopsy report is presented here was shown in this society on March 16, 1945. Since then the patient was admitted to Albert Merritt Billings Hospital several times in an attempt to reduce his weight. Clinically, no endocrine disturbances

could be demonstrated, and the obesity was thought to be caused essentially by psychogenic overeating. He had become hypertensive and had episodes of cardiac decompensation secondary to obesity. His final admission was on April 23, 1953, when he entered disoriented, drowsy, and cyanotic after a severe coughing episode. He had increasingly severe respiratory distress, and pulmonary edema, and died on the next day.

On autopsy, the main finding was diffuse basophilism of the pituitary gland, about 90% of all cells being basophilic. As far as I was able to establish, this has been the first case of juvenile acanthosis nigricans with a postmortem examination of the pituitary gland.

Discoid Lupus Erythematosus. Presented by Dr. Theodore Cornbleet, Dr. David Cohen, and (by invitation) Dr. Leonard Hoit.

Case For Diagnosis. Presented by Dr. Samuel M. Bluefarb, Dr. A. Goldberg, and (by invitation) Dr. Leonard Hoit.

Case for Diagnosis (Lichen Planus? Lupus Erythematosus? Drug Eruption?) Presented by Dr. Michael H. Ebert and Dr. Frederick J. Szymanski.

Nevus Unius Lateris. Presented by Dr. David Omens and (by invitation) Dr. Harold Omens and Dr. Leonard hoit.

Multiple Benign Plaques of the Tongue in Two Brothers. Presented by Dr. David Omens, and (by invitation) Dr. Harold Omens and Dr. Leonard Hoit.

Reticulum Cell Sarcoma. Presented by Dr. Samuel M. Bluefarb, Dr. A. Goldberg, and (by invitation) Dr. Leonard Hoit.

Lupus Vulgaris. Presented by Dr. Alfred B. Falk.

Erythema Induratum. Presented by Dr. Arthur L. Shapiro.

Sarcoidosis. Presented by Dr. Arthur L. Shapiro.

Sarcoidosis. Presented by Dr. Paul K. Weichselbaum, and (by invitation) Dr. David W. Kersting.

Granuloma Annulare. Presented by Dr. A. Buchholz and Dr. F. Kendricks (by invitation).

Pityriasis Rubra Pilaris. Presented by Dr. Stanley E. Huff.

Localized Scleroderma. Presented by Dr. Theodore Cornbleet, Dr. Sidney Barsky, and (by invitation) Dr. Leonard Hoit.

Extensive Morphea with Pronounced Pigmentation and Secondary Degenerative Phenomena. Presented by Dr. James R. Webster and (by invitation) Dr. B. J. Pass.

Systemic Blastomycosis. Presented by Dr. A. M. Buchholz.

A Case of Persistent Edema of Hands and Forearms Associated with Dermatitis. Present by Dr. Allan L. Lorincz (by invitation) and Dr. Edward H. Ferguson (by invitation).

Xanthoma Tuberosum Multiplex. Presented by Dr. Walter Klak (by invitation) and Dr. George C. Wells (by invitation).

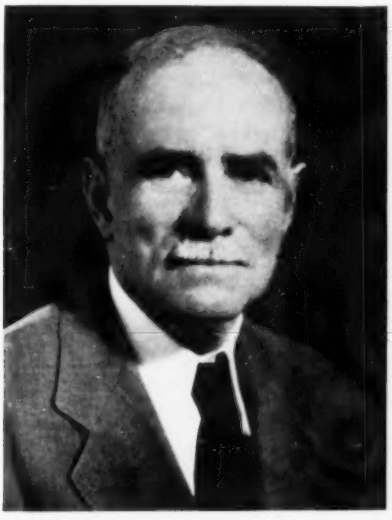
Case of Kaposi's Sarcoma. Presented by Dr. Frank J. Kendrick.

Acanthosis Nigricans, Juvenile Type. Presented by Dr. S. Rothman and (by invitation) Dr. A. L. Shapiro.

Obituaries

C. GUY LANE, M.D.
1882-1954

The sudden death on March 12, 1954, of C. Guy Lane was a shock to his numerous friends and to dermatologists world wide, and it brought to a close a very active and successful career. Born in Billerica, Mass., on Oct. 21, 1882, he was the son of Albert Clarence and Estella J. Davis Lane. He received his Bachelor of Arts degree from Harvard University in 1905, and his medical degree from Harvard Medical School in 1908. Following his internship at Worcester City Hospital,



C. GUY LANE, M.D.

1882-1954

he did general practice in Woburn until 1914, at which time he became interested in dermatology. He devoted his time so conscientiously to this specialty that he gained world-wide recognition.

A member of the Department of Dermatology of the Massachusetts General Hospital from 1919 until his death, he became chief of the department in 1936. He was also head of the Department of Dermatology at Harvard Medical School, becoming Clinical Professor Emeritus in 1947.

One of the American pioneers in the study of skin diseases due to occupation, Dr. Lane for many years was a member of the National Committee on Occupational Dermatoses. He contributed a great deal to the knowledge of industrial medicine and was a lecturer on industrial hygiene at the Harvard School of Public Health.

He held all the offices available in the New England Dermatological Society and the Section on Dermatology of both the Massachusetts Medical Society and the American Medical Association; also the American Board of Dermatology and Syphilology, the American Academy of Dermatology and Syphilology, and the American Dermatological Association. In 1949 Dr. Lane delivered the Distinguished Lecture before the Section on Dermatology and Syphilology of the American Medical Association.

His advice was sought in many fields of dermatology. He was a member of the Advisory Committee on Cosmetic Advertising, the Council on Pharmacy and Chemistry of the American Medical Association, and the Advisory Board for Medical Specialties, helping to formulate standards and examinations for this Advisory Board.

Many were his honors, including the Cutter Medal in 1948, and membership in several European dermatological societies. His contributions to dermatologic literature were voluminous, consisting of over 80 articles. He was editor of a volume on dermatology and syphilology for the Practitioners Library of Medicine and Surgery, as well as a member of the editorial board of the *New England Journal of Medicine* and the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY.

Dr. Lane's main interest was the Massachusetts General Hospital, where many excellent dermatologists were trained under his watchful eye. At one time, however, he was also connected with the Department of Dermatology at the Boston Dispensary, and he was consultant in dermatology at 16 other hospitals.

In view of his many activities it would seem that this man needed some guiding hand. This was supplied by his loving wife, Mary Rivers McHarry Lane, who was born in Hampton, Va. During his active career Mary Lane was a dear friend of dermatologists, both old and young. Also surviving Dr. Lane is his son Robert, now a lieutenant in the Air Force.

Despite his tremendous work Guy always found time to attend the various social functions connected with many dermatological meetings. Always a genial and pleasant companion at these functions, he will be missed at our future meetings.

JOHN GODWIN DOWNING, M.D.

News and Comment

ANNOUNCEMENTS

Annual Prize Essay Contest of The American Dermatological Association, Inc.—The American Dermatological Association is again offering a series of prizes for the best essays submitted for original work, not previously published, relative to some fundamental aspect of dermatology or syphilology. The purpose of this contest is to stimulate investigators to original work in these fields. Cash prizes will be awarded as follows: $500, $300, and $200 for first, second, and third place, respectively.

Manuscripts typed in English with double spacing and ample margins as for publication, together with illustrations, charts, and tables, all of which must be in triplicate, are to be submitted not later than Nov. 15, 1954. The manuscripts should be sent to Dr. J. Lamar Callaway, Secretary, American Dermatological Association, Duke Hospital, Durham, North Carolina. Those which are incomplete in any of the above respects will not be considered.

Competition in this prize contest is open to scientists generally, not limited to physicians.

The award will be made by a committee of judges selected to pass on the essays by the Research Aid Committee of the American Dermatological Association, and the decision of the judges shall be final. The essays are judged on the following considerations: (1) originality of ideas; (2) potential importance of the work; (3) experimental methods and use of controls; (4) evaluation of results; (5) clarity of presentation. This contest is planned as an annual one, but if in any year, at the discretion of the Committee and judges no paper worthy of a prize is offered, the award may be omitted.

The results will be announced prior to Jan. 1, 1955, and papers not winning a prize become the authors' property and will be returned promptly.

The candidate winning first prize may be invited to present his paper before the annual meeting of the American Dermatological Association with expenses paid in addition to the five hundred dollar prize. Further information regarding this essay contest may be obtained by writing to the Secretary of the American Dermatological Association.

The next annual meeting of the American Dermatological Association will be held April 17 to 21, 1955, at the Belleview Biltmore, Belleair, Fla.

Books

The Cutaneous Manifestations of Systemic Diseases. By John Godwin Downing. Price, $4.25. Pp. 159, with 52 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

The author has given a well-written and interesting but short review of the cutaneous manifestations of systemic diseases. The book, which contains 122 pages of text, reviews the cutaneous findings in hypersensitivities, blood dyscrasias, rheumatic, nutritional, and endocrine disorders. There is an excellent chapter showing the relationship of certain skin disorders and heredity.

The monograph is small, and as the subject is vast in scope the author, because of limitations in space, was able to give only short accounts of some of the interesting skin lesions in certain systemic diseases.

The book is not comprehensive enough for the dermatologist, but for the medical student the lack of detail will acquaint him in a general way with the skin lesions of the systemic diseases. Also, the book should help to stimulate more interest in the general practitioner in knowing more about the dermatological lesions of systemic diseases.

An Atlas of the Commoner Skin Diseases. By Henry C. G. Semon. Fourth Edition. Price, $13.50. Pp. 367, with 147 color plates. Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1953.

In the "Preface to the First Edition," the author states: "The purpose of this Atlas is to portray from the living subject, and in natural colour, a collection of the dermatoses most frequently seen in the routine of outpatient practice."

In this, the Fourth Edition, the same purpose is attempted and for the most part the plates illustrate satisfactorily the various cutaneous diseases. However, some of the illustrations are poorly chosen, and the color reproductions are not good. For example, no dermatologist could recognize urticaria pigmentosa from the illustration in this Atlas, and there are other examples quite similar. Sarcoidosis is not mentioned except in the text of Tuberculosis Nodularis.

The book is in two sections: the first illustrates the more common skin conditions, and the second, the less common diseases. Such a distinction seems questionable, for at least in the United States certain of the "common skin diseases" are seen less frequently than are those the author classifies as "less common skin diseases."

The text accompanying each plate contains brief clinical descriptions, differential diagnoses, and therapeutic suggestions. The author's remarks are interesting, especially because of many personal reminiscences.

This Atlas is recommended for the departmental or university library that has unlimited funds and for the dermatologist who enjoys collecting texts.

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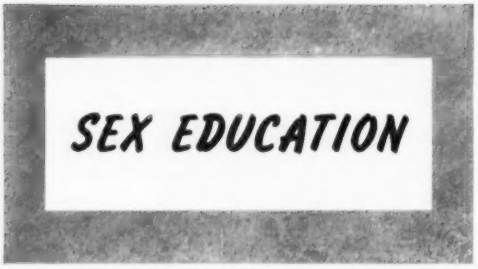

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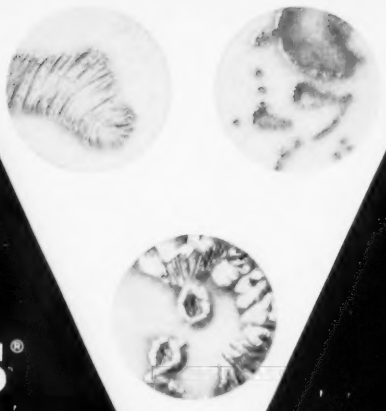

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1. Ellis, C. C., and others: The Treatment of Psoriasis with Liquor Carbonis Detergens, J. Invest. Derm. *10*:455, 1948.

2. Sulzberger, M. B., and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952, p. 323.

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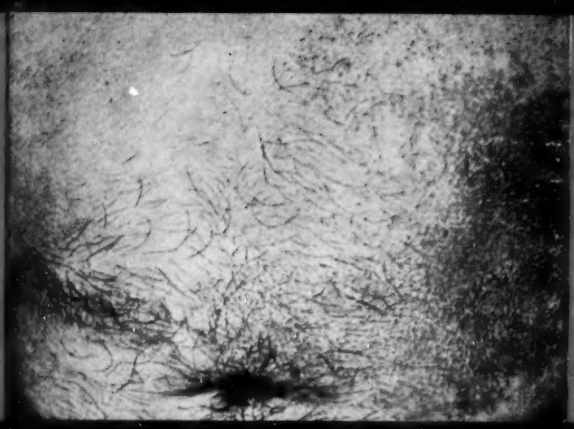

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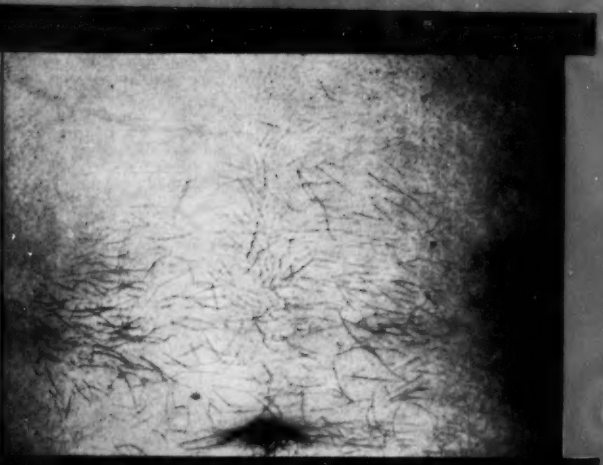

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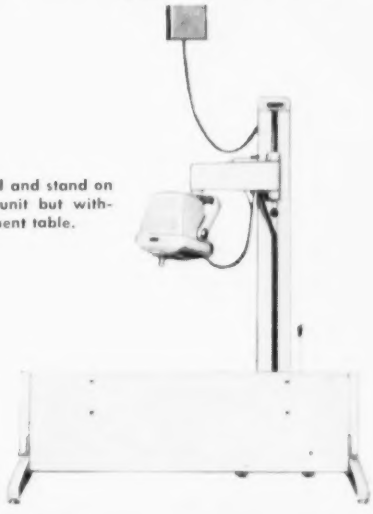

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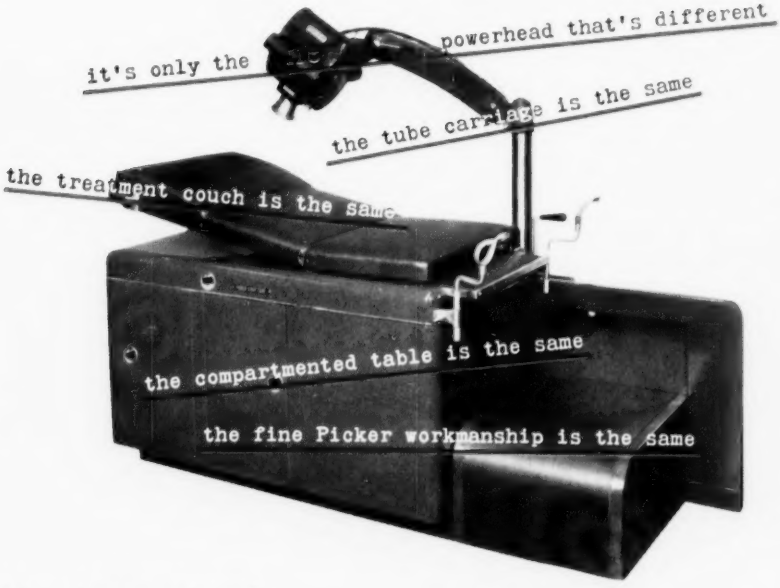
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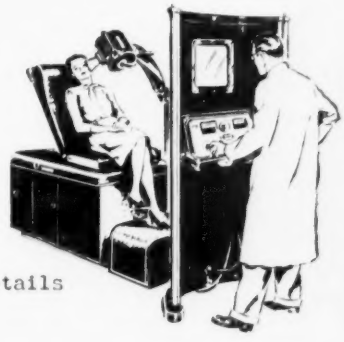

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